UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BTG INTERNATIONAL LIMITED, et al.,

Plaintiffs,

-v-

AMNEAL PHARMACEUTICALS LLC, et al.,

Defendants.

Civil Action Number:
2:15-cv-5909-KM-JBC

TRANSCRIPT OF TRIAL PROCEEDINGS

VOLUME III
Pages 494 - 750

BTG INTERNATIONAL LIMITED, et al.,

Plaintiffs,

-v-

AMERIGEN PHARMACEUTICALS, INC.,

Defendant.

Civil Action Number:
2:16-cv-2449-KM-JBC

BTG INTERNATIONAL LIMITED, et al.,

Plaintiffs,

-v-

TEVA PHARMACEUTICALS USA, INC.,

Defendant.

Civil Action Number:
2:17-cv6435-KM-JBC

MARTIN LUTHER KING BUILDING and U.S. COURTHOUSE
50 Walnut Street, Newark, New Jersey 07101
Wednesday, July 25, 2018
Commencing at 9:03 a.m.

B E F O R E:

THE HONORABLE KEVIN McNULTY,
UNITED STATES DISTRICT JUDGE

Certified as True and Correct as required by Title 28, U.S.C., Section 753
/S/ Mary-Jo Monteleone, CCR, CRCR, RPR

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(PROCEEDINGS held in open court before The Honorable KEVIN McNULTY, United States District Judge, at 9:03 a.m.)

THE COURT: Be seated. Okay. What's next?

MR. REIN: Your Honor, first we have our usual housekeeping matter of exhibits.

THE COURT: Okay.

MR. REIN: And I've got a list of exhibits that we believe should be admitted through the witnesses that we put on yesterday. I have lists. I'm happy to read them into the record or I can provide them again to the court reporter.

THE COURT: Why don't we do it the same way. Why don't you read it so it's on the record and give us the list as well.

MR. REIN: Let me start with the following PTX-exhibits, 2.2, 227, 359, 372, 383, 393, 397, 406 and 458.

Then I have the following DTX-exhibits, 1235, 1260, 1276, 1278, 1323, 1331, 1333, 1338, 1336, 1340, 1354, 1367, 1358 -- sorry about that being out of order -- then I have DTX-1573, 1575, 1580, 1585 and 1707.

Oh, I've been corrected on one thing. I started out by saying that the first grouping were the PTX-exhibit. In fact, the first one was PDX.

THE COURT: PDX, I thought that was what you said, actually.

MR. REIN: That, I think, that brings me to the DTXs.

DTX-1573, DTX-1575, DTX-1580, DTX-1585 and DTX-1707.

And lastly, the JTX-exhibits.

THE COURT: Now I'm confused. Where was the break between the PTX and the DTX?

MR. REIN: Good point. I thought I was picking up from where I read before. But do you have 1235, 1260?

THE COURT: Yes.

MR. REIN: All the way to 1358?

THE COURT: All the way to 1707.

MR. REIN: All the way to 1707. Then we're all set.

THE COURT: Okay. Okay.

MR. REIN: I probably read some of them twice.

THE COURT: Okay. Now you have the joint.

MR. REIN: Joints are JTX-8002, 8005, 8011, 8093, 8123, 8128, 8145, 8187 and 8102.

And I have a copy of the listing. Hopefully, I hope I didn't misspeak. I'll have to go share it with the court reporter so she takes it down accurately.

THE COURT: Okay. Why don't you give her a copy for her reference.

MR. REIN: Would you like one, Your Honor?

THE COURT: I don't need a separate one, no.

MR. REIN: And then, lastly, if the defendants don't have anything, we're prepared for the redirect.

THE COURT: Mr. Wong.

MR. WONG: No objection, and that covers the list that we had too.

THE COURT: So that's it. All right. Those -- those exhibits that's listed will be admitted.

(Exhibit Nos. PDX 2.2, 227, 359, 372, 383, 393, 397, 406 and 458 are received are evidence.)

(Exhibit Nos. DTX 1235, 1260, 1276, 1278, 1323, 1331, 1333, 1338, 1336, 1340, 1354, 1367, 1358, 1573, 1575, 1580, 1585 and 1707 is received are evidence.)

(Exhibit Nos. DTX 1235, 1260, 1276, 1278, 1323, 1331, 1333, 1338, 1336, 1340, 1354, 1367, 1358, 1573, 1575, 1580, 1585 and 1707 are received in evidence.)

(Exhibit Nos. JTX 8002, 8005, 8011, 8093, 8123, 8128, 8145, 8187 and 8102 are received in evidence.)

THE COURT: Any further housekeeping before we begin? Okay. Are we set?

MR. REIN: I believe we are, Your Honor.

THE COURT: Okay. Is it Ms. O'Shea or Dr. Rettig?

MR. REIN: It will be Ms. O'Shea.

THE COURT: Okay.

MS. DONOVAN: Good morning, Your Honor.

THE COURT: Good morning.

MS. DONOVAN: Bindu Donovan again from Sidley Austin.

SUZANNE O'SHEA, PLAINTIFF'S WITNESS,

having been duly sworn, testifies as follows:

REDIRECT EXAMINATION

BY MS. DONOVAN:

Q. Good morning, Ms. O'Shea.

A. Good morning.

Q. Ms. O'Shea, the defendants tried to suggest on cross that your opinions on whether the patent claims are off-label use or on-label, were not based on the Court's claim construction. Do you recall that?

A. Yes, I do.

Q. Do you recall that the defendants played your deposition testimony from July 2017?

A. Yes, I do.

Q. Did you submit supplemental expert reports in this case addressing defendants' amended ANDA labels?

A. Yes.

Q. If you could, please turn to DTX-1584.

A. I don't have that book.

MS. DONOVAN: May I approach, Your Honor?

THE COURT: Sure.

THE WITNESS: Thank you.

BY MS. DONOVAN:

Q. Ms. O'Shea, if you could turn to DTX-1584. Is this your expert report from May 2018?

A. Yes, it is.

Q. Please turn to Page 5, Paragraph 10 of your expert report.

A. Yes.
Q. Does Paragraph 10 indicate whether you were informed of this Court's claim construction?
A. Yes, it does.
Q. And you were informed of your -- of the Court's claim construction at the time you submitted your supplemental expert report?
A. Yes, I was.
Q. In reaching the opinions you expressed yesterday, did you apply the Court's claim construction?
A. Yes, I did.
Q. Did defendants take your deposition after you submitted your expert report on the amended labels, after you submitted your supplemental expert report?
A. Yes, I believe so.
Q. And your testimony that the defendants played relating to the Court's claim construction came from 2017, not from your 2018 deposition relating to the amended ANDA product labels, correct?
A. I think there was, maybe, one from the 2018 deposition, but the others were all from the earlier deposition, correct.
Q. But the specific testimony that the defendants played, trying to suggest on cross that your opinions on the patent claims being an off-label or on-label use, were not based on the Court's claim construction, that testimony was from 2017,

not from your 2018 deposition?
A. I believe that's correct.
Q. And just to refresh us, your opinion yesterday was that the '438 patented method of treatment is not an off-label use. Is that right?
A. Yes, my opinion is that the method of treatment in the patent, as construed by the Court, is not an off-label use, correct.
Q. Ms. O'Shea, staying with that, the testimony that the defendants played from your deposition in July 2017, that concerned the fact that you weren't aware of the Court's claim construction that abiraterone and prednisone both have an anti-cancer effect in the combination at that time, correct, in July of 2017?
A. That's what the testimony concerned. That's -- well, that was the defendants' position, yeah.
Q. And subsequently, after your first deposition, you wrote two supplemental expert reports, as we've just discussed?
A. Yes.
Q. And at that time you looked at more regulations?
A. Yes.
Q. And among other things, you located 21CFR.57, a section that you mentioned on direct yesterday?
A. 201.57?
Q. Yes.

A. Yes.
Q. And as you advised yesterday, that regulation states that when FDA approves a drug for symptoms or palliation, or as an adjunct therapy to another drug, it should clearly state that?
A. That's correct.
Q. After submitting your supplemental expert reports, the defendants took your deposition again. We just discussed that?
A. Yes, hmm-hmm.
Q. And all but one of the clips that they showed to impeach you were in the first deposition before your Court -- before you addressed your -- your report addressed the Court's claim construction?
A. That's right.
Q. The only testimony that the defendants played from the second deposition asked if it was your understanding that FDA required --
THE COURT: Listen, I'm going to have to ask you -- this is your witness. Okay? You're leading a lot.
MS. DONOVAN: Okay.
THE COURT: Okay?
MS. DONOVAN: I'll rephrase.
BY MS. DONOVAN:
Q. Ms. O'Shea, the defendants also played testimony from the second deposition in which you were asked if it was your understanding that FDA required prednisone to be taken with

abiraterone acetate for a particular purpose?
A. Yes.
Q. Does that have anything to do with whether the label is saying prednisone, in the combination, has an anti-cancer effect?
A. Could you please restate what the -- what part the deposition said?
Q. Yes. Ms. O'Shea, yesterday the defendants played a clip from your second deposition --
A. Hmm-hmm.
Q. -- in which you were asked if it was your understanding that FDA required prednisone to be taken with abiraterone acetate for a particular reason?
A. If FDA understood that?
Q. That was the question.
A. Okay.
Q. Yes. The question you were asked is, is it your understanding that FDA required prednisone to be taken with abiraterone acetate for a particular reason?
A. Okay.
Q. Does that have anything to do with whether the label is saying prednisone, in the combination, has an anti-cancer effect?
A. Whether the label for -- has a -- does it have anything to do with whether the approved label says that prednisone has an

anti-cancer effect?

Well, when FDA approved the indication statement, they said that abiraterone and prednisone together are intended for the treatment of prostate cancer.

Q. Thank you. Ms. O'Shea, do you recall being asked questions about Zytiga marketing materials yesterday?

A. Yes, I do.

Q. Can marketing materials change what is in the Zytiga label?

A. No.

Q. And I got the sense yesterday from the defendants' questions that Zytiga puts -- that Janssen puts out no marketing materials that promote the efficacy of the combination of abiraterone acetate and prednisone. Is that a true statement?

A. I'm not familiar with all of Janssen's marketing materials for Zytiga. The ones I was shown yesterday seem to focus on prednisone.

Q. Have you seen other marketing materials in which Janssen does promote the efficacy of the combination of abiraterone acetate and prednisone?

A. I don't believe I have.

Q. If you could, please look at PTX-424.

MS. DONOVAN: And, Your Honor, we have some courtesy copies for the Court and for the defendants' attorneys. Would

the Court like courtesy copies? Would the Court like a copy of what has been displayed?

THE COURT: Sure. This is not in the book, I take it?

BY MS. DONOVAN:

Q. Ms. O'Shea, please look at Plaintiff's Trial Exhibit 424.

A. Okay.

Q. Do you understand that this is a marketing material for Zytiga plus prednisone?

A. It -- yes, it looks that way.

Q. In this marketing material, does Janssen promote the combination of abiraterone acetate plus prednisone based on the survival benefit of the combination?

A. Right at the top it says, Zytiga plus prednisone achieved a statistically significant median overall survival difference.

Q. And I'd also like to show you Plaintiff's Trial Exhibit 447.

MS. DONOVAN: May I approach, Your Honor?

THE COURT: Yes. This also is one not in the book?

MS. DONOVAN: Yes.

BY MS. DONOVAN:

Q. Ms. O'Shea, do you recognize Plaintiff's Trial Exhibit 447 as another example of Zytiga marketing materials?

A. Yes, I do.

Q. And does Plaintiff's Trial Exhibit 447 also promote the use of abiraterone acetate plus prednisone based on an overall

survival benefit in the combination?
A. Yes. It says Zytiga plus prednisone significantly increased median radiographic progression for survival.
Q. Ms. O'Shea, do marketing materials have a different purpose than drug product labelling?
A. Yes, they do.
Q. Do marketing materials need to provide a fair and balanced description of the drug or therapy?
A. Yes, they do.
Q. As a result, do marketing materials typically provide a description not only of the benefits of the drug or therapy, but also the contraindications and possible side effects?
A. Yes, FDA requires a fair balance.
Q. Do marketing materials have to be consistent with the approved indication for the drug?
A. Yes, they do.
Q. Is there any requirement that marketing materials be limited to the indications and usage section of the drug product labelling?
A. That's a question that lots of people spend lots of time on. It's an issue currently under a great deal of discussion.

Marketing manufacturers are able to provide truthful and non-misleading information. They are required to restate the indicated -- the approved indication and use from the approved label in their marketing material.

Q. Let me clarify my question. If a drug has benefits in addition to the benefits in the approved indication, is it appropriate to describe those additional benefits in the drug's marketing materials, as long as it is truthful and not misleading?
A. Well, again, there's currently a great deal of debate about that, but in general, manufacturers can provide truthful and non-misleading information about their products.
Q. So just to summarize that, if a drug has benefits in addition to the benefits in the approved indication, it's appropriate to describe those additional benefits in the drug's marketing materials if they are truthful and non-misleading?
A. Well, in addition to being truthful and non-misleading, they should be supported by substantial evidence.
Q. You testified yesterday that under FDA regulations, if a drug's intended to treat symptoms or treat the side effects of another drug, it should be stated clearly in the indication statement, correct?
A. That's right.
Q. Does that mean that under FDA regulations, if a drug is intended solely for managing symptoms or to treat side effects of another drug, that should be stated clearly in the indications and usage?
A. I would expect that, yes, and that's consistent with 201.57C something.

Q. Does the indications and usage section of the Zytiga label preclude the use of prednisone with abiraterone acetate for additional benefits?
A. Preclude the use of it?
Q. Correct.
A. No, it doesn't preclude the use of the product.
Q. To the extent that the use of prednisone with abiraterone acetate has the additional benefit of managing potential side effects, is Janssen permitted to explain that safety role in its marketing materials?
A. As long as it was truthful and not misleading, and that there was substantial evidence supporting that.
Q. Okay. Do you recall being asked whether prednisone was ever approved as a monotherapy for treating prostate cancer?
A. I believe I was asked that, yes.
Q. Does that have anything to do with whether the Zytiga labelling instructs that abiraterone and prednisone be given to treat mCRPC?
A. No, it's not a requirement that it be approved separately.
Q. All defendants say is missing from the Zytiga label is an expressed statement that prednisone is providing an anti-cancer effect. You testified several times yesterday that the Zytiga label does in fact indicate that the indications and usage section -- in the indications and usage section, that both abiraterone acetate and prednisone, when used in combination,

provide an anti-cancer effect?
A. Yes.
Q. Is that equally true of defendants' proposed ANDA product labels?
A. Yes. They're essentially identical to the Zytiga label.
Q. If the claims require, in addition to requiring that the same drugs, the same amounts, and the same disease -- let me withdraw that.

If the claims require, in addition to the same drugs, the same amounts, and the same disease, that both abiraterone acetate and prednisone provide anti-cancer effects, do the Zytiga 2018 label and defendants' labels do that?
A. Yes, in the indications and use section.
Q. Does that mean that even under defendants' own view of what the claims require, that the indicated use is on-label?
A. Well, I'm not sure I want to say -- I'm not sure I'm clear on what the -- I wouldn't want to speak for the defendants here. But I would say that the claims from the '438 patent are on-label, in that the indications and usage section indicates that both abiraterone acetate and prednisone are intended to treat prostate cancer, meaning that they are intended to treat the disease itself.
Q. Does the indications and usage section of the Zytiga label contain any indications other than prostate cancer?
A. No.

Q. Would FDA permit any other indications or uses to be implied or suggested from other sections of the labelling that are not set forth in the indications and usage section of the Zytiga label?
A. No. The regulations explicitly state that other sections of the label may not suggest or imply other indications, other than those that are stated in the INU section.
Q. Defendants' counsel yesterday showed you some documents that they said described additional potential side effects of abiraterone acetate, correct?
A. Additional potential side effects?
Q. Additional side effects. Let me ask you that again.
The defendants' counsel showed you some documents that allegedly described side effects of abiraterone acetate?
A. Yes, yeah. I was stumbling over the "additional" part.
Q. If FDA thought those additional side effects were a problem, FDA would have inserted them into the label?
A. Yes. Or they would have required that Janssen put them in the label.
Q. And the defendants' counsel, yesterday, asked you some questions concerning the requirement that FDA approved indications be supported by substantial evidence of effectiveness based on adequate and well-controlled clinical studies?
A. Yes.

Q. In evaluating clinical studies supporting the efficacy of therapies, such as of Zytiga plus prednisone, the FDA assesses the efficacy of the therapies, correct?
A. Yes, that's right.
Q. And the approved therapy here is abiraterone acetate plus prednisone, correct?
A. Abiraterone was approved for use in combination with prednisone in the treatment of prostate cancer, right.
Q. What do the clinical studies show concerning what therapy was evaluated by the FDA for efficacy?
What do the clinical studies show concerning what therapy was evaluated by the FDA for efficacy?
A. Well, basically, the trial design of the phase III clinical trials in the active treatment arm, patients got abiraterone plus prednisone.
Q. And so that's what FDA evaluated?
A. That's what FDA evaluated.
Q. Ms. O'Shea, defendants' counsel, also, showed you some documents relating to the clinical development of Zytiga, such as the April 2005 pre-IND meeting minutes?
A. Yes.
Q. Does the pre-IND meeting occur very early in the drug development process?
A. Yes, by definition, a pre-IND meeting is held before the IND is granted and then IND is granted to give a company

permission to conduct a clinical trial.
Q. Just to clarify, explain that fully, would a pre-IND meeting occur before or after any clinical trials have begun?
A. They would occur before whatever clinical trial was being discussed. A company can have more than one pre-IND meeting before every clinical trial, but it's before the clinical trial is conducted.
Q. Does information discussed during a pre-IND meeting reflect the final conclusions of FDA?
A. No. No, it reflects FDA's thinking at that time. And the purpose of a clinical -- a pre-IND meeting is to -- or the purpose of an IND is to determine whether the study is safe to go forward.
Q. Is information discussed during a pre-IND meeting necessarily incorporated into the clinical development plan for a drug?
A. Not necessarily, no.
Q. Can the ultimate phase I clinical trial design end up being very different from what is discussed in an early meeting, such as a pre-IND meeting?
A. Yes. FDA gives its -- gives its views and its feedback, but it's up to the company to decide whether or not to take that feedback.
Q. Do the phase III studies establish that abiraterone acetate and prednisone, in combination, establish the efficacy

of the combination to treat prostate cancer?

A. Well, again I am --

MR. KLEIN: Objection, lack of foundation.

THE COURT: Repeat that question for me. I didn't get it either, frankly. Or you can rephrase it, if you like.

MS. DONOVAN: Sure.

BY MS. DONOVAN:

Q. Ms. O'Shea, based on your FDA expertise, do the phase III clinical studies establish that abiraterone acetate and prednisone, in combination, supported the efficacy of the combination to treat prostate cancer?

THE COURT: Let me slow you down. Are you asking a scientific opinion here? I'm not sure what the question is.

MS. DONOVAN: I'm asking based on Ms. O'Shea's reviews of the clinical studies.

THE COURT: You're saying if you were a regulator, what would you think?

MS. DONOVAN: Yes.

THE COURT: I'll permit it for that limited purpose.

Sorry, Ms. O'Shea, have you lost track of the question?

THE WITNESS: Well, my personal view, I haven't reviewed the clinical trial, personally. I am relying on FDA's conclusion as reflected in the indications and usage section that abiraterone acetate and prednisone, together, are

effective in the treatment of prostate cancer.

THE COURT: You know, I sort of thought that's what you were going to say, for some reason. And I think we've gotten as far as we can with an answer to that question.

I mean, if you're saying, what would you do if you were the FDA and she says, well, I'm relying on what the FDA did, I think we've come full circle. So let's move on.

BY MS. DONOVAN:

Q. Ms. O'Shea, defendants are suggesting, based on the phase III clinical studies, that prednisone's contribution could be zero. You were asked that yesterday, that hypothetical?

A. Yes, I was asked that yesterday.

Q. Could FDA have looked to the phase I and 2 studies to support a conclusion that both prednisone and abiraterone acetate are contributing to efficacy?

A. Sure, FDA will look at all of the data that is submitted to it in the NDA.

Q. The FDA wants the most efficacious use to be made, if it is safe?

A. Yes, FDA's goal is to protect the public health to the maximum extent justified.

Q. If so, and if prednisone contributes to the efficacy of the combination in the phase II study, then as a matter of policy, would FDA want to make sure that clinicians use abiraterone acetate and prednisone together for efficacy?

MR. KLEIN: Objection, leading.

THE COURT: It is, but, look, it's an expert witness. I'll permit it in the interest of moving it along. I'll permit you to answer in that form.

THE WITNESS: I mean, as a matter of policy, FDA wants physicians to have as complete information as possible in order to know what they're prescribing.

BY MS. DONOVAN:

Q. And if FDA -- if prednisone contributes to the efficacy of the combination in the phase II study and FDA wants to make sure that clinicians use the drug together for efficacy, is the best way to do that --

THE COURT: What's the best way to do that?

MS. DONOVAN: What is the best way to do that?

THE WITNESS: To be as clear as possible in the approved instructions for use.

BY MS. DONOVAN:

Q. And that would mean saying that the indication would be abiraterone acetate plus prednisone to treat prostate cancer?

A. In combination for the treatment of prostate cancer.

THE COURT: So we've heard. Okay. Let's -- if we are just going to repeat the indications section over and over, perhaps this isn't the best use of our time.

MS. DONOVAN: I understand, Your Honor.

Your Honor, I don't have any additional questions.

THE COURT: Okay. Thank you. There's some new material. Is there some recross you would like to offer?

MR. KLEIN: Yes, Your Honor.

THE COURT: Confine yourself to what's new about the redirect, obviously.

MR. KLEIN: Thank you.

RECROSS-EXAMINATION

BY MR. KLEIN:

Q. Hello, Ms. O'Shea.

A. Good morning.

Q. First of all, did you speak to counsel after court ended yesterday to prepare for your redirect?

A. Not a single word.

Q. Okay. I want to talk about the submission of the reports, because that came up on the redirect. Do you remember that?

A. Yes.

Q. Okay. And, initially, you submitted a primary expert report during the typical expert discovery, right?

A. Yes.

Q. And in that report you included all of your opinions with regard to the 20 -- what we were calling the 2015 Zytiga label, right?

A. Yes.

Q. And then you were deposed?

A. Yes.

Q. And some of the deposition was played yesterday, right?
A. Correct.
Q. And then earlier this year, Janssen amended its Zytiga label and we called it the 2018 Zytiga label; is that right?
A. That's right.
Q. And you submitted a supplemental report or, actually, two of them, right?
A. Yes -- well, one was very short but one, yeah.
Q. An initial report and then a reply?
A. Yes.
MR. KLEIN: Mr. Russell, can you put up DTX-1584.1, please?
BY MR. KLEIN:
Q. Is this a copy of your supplemental report, the first one which is marked DTX-1584?
A. You know, I go by the dates on these things.
Q. Well --
A. So I'm going to assume it is.
Q. Well, I'll represent to you that that's your supplemental report.
A. Okay.
Q. Can we go to .4 of the document. Okay.
MR. KLEIN: And can we highlight Paragraph 3, please.
BY MR. KLEIN:
Q. Now, this paragraph says, You understand from counsel for

the plaintiff that on April 10th, 2018, the Court ordered the parties to conduct supplemental expert discovery concerning the effects of the FDAs approval of an updated label for Zytiga and the defendants' submission of an updated proposed ANDA, right? I paraphrased towards the end.

A. Yes.

Q. In essence, the purpose of the supplemental report was to address the changes between the 2015 and 2018 labels, right?

A. That's correct.

Q. And yesterday you testified that the revised indication in the 2018 Zytiga label with respect to the CRPC -- sorry.

Okay. Yesterday you testified that the revised indication in the 2018 label with respect to the CRPC indication is the same as the 2015 label, right?

A. Yes.

Q. And then you were deposed after your supplemental reports, right?

A. That's right.

Q. And I asked you if you stood by your earlier testimony and you said yes, right?

A. Yes.

Q. On redirect, counsel referred you to two marketing documents, PTX-424 and PTX-447, right?

A. Are these pieces that I have here?

Q. Yes.

THE COURT: Yes. You're not expected to memorize the exhibit numbers, obviously. The two green ones, right?

THE WITNESS: Okay.

BY MR. KLEIN:

Q. So yesterday, as you mentioned on redirect, we looked at some marketing materials that focused on the role of prednisone in the Zytiga indication, right?

A. Yes.

Q. Those two documents in front of you, they don't focus on the role of prednisone in the Zytiga indication, correct?

A. I haven't had a chance to really thoroughly read these, but at first blush, it looks like they are talking about the combination of abiraterone acetate plus prednisone.

Q. And, also, on redirect, counsel asked you whether FDA would consider phase I and phase II trials that were submitted during the application process, right?

A. Yes.

Q. Okay. But FDA, typically, does not rely on phase I and 2 studies as adequate and well-controlled studies sufficient to support an FDA drug indication, correct?

A. Phase I and 2 studies are, typically, not adequate and well-controlled studies, but FDA can certainly use the information learned from phase I and phase II to inform its approval decision and inform how it interprets the phase III trial.

Q. Okay. Right. But FDA wouldn't rely on just the results from a phase I or 2 study to support a new indication, correct?
A. Typically, not. I mean -- you know, FDA -- FDA's overriding purpose is to support the public health and promote the public health and if --
Q. I think you answered.
MR. KLEIN: No further questions, Your Honor, thank you.
THE COURT: All right.
You may step down, Ms. O'Shea. Thank you.
(Witness excused.)
THE COURT: Okay. I think you said Dr. Rettig would be next.
MR. REIN: That is correct, Your Honor, and Todd Krause will put on the witness.
THE COURT: Okay.
MATTHEW RETTIG, M.D., PLAINTIFF'S WITNESS,
having been duly sworn, testifies as follows:
DIRECT EXAMINATION
BY MR. KRAUSE:
MR. KRAUSE: Can we approach, Your Honor?
THE COURT: Yeah, you can hand up whatever notebooks you've got.
MR. KRAUSE: May I proceed?
THE COURT: Yes. Introduce yourself and go ahead when

you're ready.

MR. KRAUSE: Thank you, Your Honor. Todd Krause of Sidley Austin. I'd like to provide a background for Dr. Rettig.

THE COURT: Yeah, we'll do it in the same manner as was done for Ms. O'Shea, that is I'll permit you to --

MR. KRAUSE: Yes, Your Honor.

THE COURT: I assume there's no particular dispute about the background and qualifications of Dr. Rettig. So I'll permit you to deliver the equivalent of an oral CV and he'll say whether you're telling the truth about him or not.

MR. KRAUSE: Thank you, Your Honor.

Dr. Matthew Rettig is an expert in medical oncology and the treatment of prostate cancer with over 25 years of experience treating prostate cancer, including metastatic castration-resistant prostate cancer.

Dr. Rettig is currently the medical director of the Prostate Cancer Program of the Institute of Urologic Oncology at UCLA School of Medicine. He is, also, a professor at the Department of Medicine and the Department of Urology at the UCLA School of Medicine, and Chief of Division of Hematology Oncology for the Veterans Administration, Greater Los Angeles Health Care System in West Los Angeles.

Dr. Rettig further served as the Director of the Operation Men's Project to enhance cancer care for Veterans, a

collaboration between UCLA and the VA Greater Los Angeles Health Care System, to enhance cancer care for Veterans.

Dr. Rettig received a Bachelor of Arts in chemistry from Wesleyan University in 1986, and an M.D. from Duke University of Medicine in 1990.

Dr. Rettig was Board Certified in Internal Medicine in 1991, and he has been Board Certified in Medical Oncology since 1998.

Dr. Rettig has been active in medical practice since 1991, including completing his internship in internal medicine at the University of Southern California Los Angeles.

His residency in internal medicine at the University of Washington Seattle, and fellowship in hematology oncology at the UCLA School of Medicine.

Dr. Rettig has served as a principal investigator in several clinical trials related to the treatment of prostate cancer, and has both clinical and laboratory research programs. As director of the clinical trials program in prostate cancer at UCLA, Dr. Rettig has conducted multiple prostate clinical trials that span the spectrum of the stage of disease. From neoadjuvant therapies, to post-chemotherapy, castration-resistant disease.

In his laboratory research program, which includes programs funded by the NIH, Prostate Cancer Foundation, American Cancer Society, Department of Defense and the

Department of Veterans Affairs, is focused on identifying biochemical targets for drug development and castration-resistant prostate cancer and kidney cancer.

Dr. Rettig has received 50 research grants and fellowships; more than 15 of which are currently active, and most of which relate to prostate cancer. He is also an author of over 50 peer reviewed papers which have been published or accepted for publication, many relating to treatment of prostate cancer.

At least 90 percent of Dr. Rettig's medical practice involves patients with prostate cancer; 80 to 90 percent of whom have metastatic castration-resistant prostate cancer.

Dr. Rettig has personally prescribed the combination of abiraterone acetate and prednisone to numerous metastatic castration-resistant prostate cancer patients since approval of abiraterone acetate and prednisone in 2011.

In addition to his medical practice, Dr. Rettig has served on a number of advisory committees relating to oncology and urology. Among other things, he was a full-time member of the VA merit review oncology age study section (Genitourinary Prostate Cancer Section), a director of the Multidisciplinary Tumor Board for VA-West LA, a grant reviewer for the Prostate Cancer Foundation, and the Tower Cancer Research Foundation, and chairman of the board of directors for the Brentwood Biomedical Research Institute, which is a non-profit grant

making organization for the VA.

Dr. Rettig is also co-chairman of the steering committee of the Prostate Cancer Foundation (PCF)- VA strategic partnership, known as the Precision Oncology Program Cancer of the Prostate (POPCAP) which is part of Vice President Joseph Biden's National Cancer Moonshot effort, overseeing $50 million in research funding over the next five years.

Dr. Rettig has received various awards, including the Creativity Award from the Prostate Cancer Foundation in 2010 and 2011, the Challenge Award from the Prostate Cancer Foundation in 2012, the STOP Cancer Award, the Jerry Janger Memorial Seed Grant in 2015, and the VALOR Award, also from the prostate cancer foundation.

BY MR. KRAUSE:

Q. Dr. Rettig is this an accurate summary of your credentials?

A. Yes. I think since that CV was submitted I have, possibly, 10 additional peer review publications.

MR. KRAUSE: Your Honor, the plaintiffs offer Dr. Rettig as an expert in medical oncology and the treatment of prostate cancer.

THE COURT: Any objection?

MR. KLEIN: No objection.

THE COURT: Okay. Dr. Krause is, obviously, well credentialed and qualified to offer an opinion in this area. I

take it, by the way, that he personally was not involved in the events in suit, that is, obtaining FDA approval for this drug or obtaining the patent, correct?

MR. KRAUSE: That's our understanding, Your Honor.

THE COURT: Okay. So peer expert testimony. Go ahead.

BY MR. KRAUSE:

Q. Dr. Rettig, have you ever testified as an expert at trial before?

A. No, this is my first time.

Q. Do you understand the defendants are seeking FDA approval to market generic abiraterone acetate tablets?

A. Yes.

Q. Have you analyzed whether defendants will induce infringement and contributorily infringe the asserted 438 patent claims if their generic products are approved?

A. Yes.

Q. What conclusions did you reach?

A. That they will indeed induce infringement and contributorily infringe.

Q. Before we go into the infringement issues in detail, let's start with some brief technical background.

What is the prostate?

A. The prostate is a male genitourinary organ. It's located in the pelvis. It produces a fluid that is stored and release

with semen as a way of sort of lubricating the sperm.
Q. And what is prostate cancer?
A. Prostate cancer is an abnormal growth that is derived in the prostate and derived from normal prostate tissue.
Q. What is metastatic prostate cancer?
A. Metastatic means the tumor has escaped from the primary sight, in this case the prostate, and gone to another organ such as the bones, liver, lung. Like those.
Q. What are androgens?
A. Androgens is the term for male hormones. They include many, but the most dominant one in an intact adult male is testosterone.
Q. Where are androgens produced in the body?
A. So androgens are most commonly produced in the testicles of an adult male. About 95 percent of circulating androgens are attributable to the testes. The testes is the only organ that physiologically produces testosterone. There are some androgens that are produced in the adrenal glands but they're weak androgens and they are not testosterone.
Q. What role do androgens play in prostate?
A. In normal prostate they maintain the viability of the organ. In malignant prostate cancer the androgens overwhelmingly are key growth factor for the cancer that promotes its survival and proliferation.
Q. How do androgens interact with prostate cells?

A. So androgens enter the tumor cell and they interact with something called the androgen receptor, or AR, and that interaction is what ignites the androgen receptor. It's sort of the key in ignition and the engine concept. So the androgen gets into the tumor cell, turns the key and the engine, the androgen receptor is activated. That androgen receptor, in turn, what it does is it's called a transcription factor. It means it regulates genes, and the genes that it regulates in a tumor cell are genes that promotes its survival and proliferation.

Q. What happens if androgens are withdrawn from normal prostate cells?

A. So that -- that -- that -- that signal, that key in the ignition, if you will, is turned off. So the androgen receptor becomes inactivated and all the genes that promote survival and proliferation are no longer expressed and the tumor cell will shrink and die.

Q. How is metastatic prostate cancer usually treated?

A. Metastatic prostate cancer is almost always initially treated with androgen deprivation, ADT. Which is essentially castration. Which can be achieved either medically or surgically, as has been discussed.

Q. I'm sorry, Doctor. Did you refer to androgen deprivation therapy as ADT?

A. ADT, yes. Thank you.

Q. And how is ADT performed?
A. So it can be done medically or surgically. Surgical castration is removal of both testicles. Medical castration involves the periodic injection of something called LHRH analogues. And, essentially, what they do is shut off the normal signal from the brain, the pituitary gland, to the testes that triggers androgen production in the testes.
Q. And what is the goal of ADT with respect to the interaction of androgens with prostate cancer cells?
A. It's shutting off the, at least initially, what is the dominant source of androgens, the testicles. That's the purpose.
Q. Does ADT cure metastatic prostate cancer?
A. No, it's not a curative therapy.
Q. And what is castration-resistant prostate cancer?
A. It is the term that we've been talking about. It indicates some measure of progression of the cancer, worsening of the cancer, despite castrate levels of serum testosterone.
Q. And what is metastatic castration-resistant prostate cancer?
A. That's just the combining of the term metastatic and castration. So metastatic being the anatomic word, the spread of the cancer, and castration being the state, meaning the tumor is no longer -- it can continue to grow despite castrate levels of serum testosterone.

Q. Is metastatic castration-resistant prostate cancer sometimes referred to as mCRPC?
A. Yes.
Q. Do you treat mCRPC patients in your medical practice?
A. Yes.
Q. What therapy do you most often prescribe to your patients to treat the mCRPC?
A. So the patients are already on androgen deprivation therapy castration and, interestingly, they stay on that. But the next step, the most common therapy that I personally prescribe is Zytiga, in combination with prednisone.
Q. Could you please turn to JTX-8000 in your binder?
A. One second. Got it.
Q. Do you recognize JTX-8000 as a copy of the 438 patent?
A. I do.
Q. Do you understand plaintiffs are asserting claims 4, 8, 11, 19 and 20 of the 438 patent against defendants?
A. Yes.
Q. You mentioned earlier that you have concluded that the defendants will induce and contribute to infringements of the asserted claims if their ANDA does get approved. Have you prepared a demonstrative listing of principal materials that you considered in your infringement analysis?
A. Yes.
Q. If we could please display PDX 4.2. What are the

principle materials that you considered?
A. As shown here, the 438 patent. The Court's opinion on the marketing patent claim construction. The parties agreed claimed constructions, the defendants proposed labels, the Zytiga label from 2011, 2012, 2015 and 2018, documents referenced by the defendants' experts, and then the depositions of Drs. de Bono, Charnas, Lee, Louis Langas and the defendants' representatives.
Q. Have you also prepared a demonstrative to summarize the legal principles you were asked to follow in reaching your opinions on infringement?
A. Yes.
MR. KRAUSE: If we could display PDX 4.3.
Q. And what are the legal principals that you applied in your analysis?
A. Shown here, there's principal of direct infringement, induced infringement, and contributory infringement.
Q. And what legal principles relate to direct infringement?
A. The person who performs all of the steps of a claimed method.
Q. What are the principles related to induced infringement?
A. Defendant has knowledge of the patent, direct infringement by another person will occur, and the defendant knowingly induces that infringement and has specific intent to encourage that infringement.

Q. And finally, what are the principles relating to the contributory infringement?
A. Again, the defendant has knowledge of the patent, direct infringement of the patent method using a component supplied by the defendant, the component is a material part of the invention, and finally, the defendant knows the component is especially made or adapted for infringement, not suitable for substantial non-infringing uses.
Q. Do you understand that the Court has interpreted some of the claim terms, and the parties have agreed on the interpretation of other terms?
A. Yes.
Q. Did you apply those claimed construction in performing your infringement analysis?
A. Yes.
Q. Did you analyze infringement from the perspective of a person of ordinary skill?
A. Yes.
Q. Have you offered an opinion on the definition of a person of ordinary skill in this case?
A. Yes, I have.
Q. Have you prepared a demonstrative with your definition of a person of ordinary skill?
A. Yes.
MR. KRAUSE: If we could please look at PDX 4.9.

BY MR. KRAUSE:

Q. In your opinion, what is the definition of a person of ordinary skill?

A. Described here. A person of ordinary skill would be a physician specializing in urology or medical oncology who has significant practical experience in the treatment of patients with prostate cancer. Such a person would've worked in a team or setting that includes access to one or more individuals who have expertise in endocrinology, biochemistry, pharmacology and/or molecular biology, or related field of science, and who has experience in prostate cancer treatments or androgen synthesis and action.

Q. Are you familiar with defendants definition of a person of skill?

A. Yes.

Q. If defendants' definition of a person of skill were applied, would any of your opinions on infringement change?

A. No.

Q. Before we talk about infringement in depth, let's briefly discuss what the asserted claims cover, starting with claim 11.

Have you prepared a demonstrative showing claim 11 and the claims from which it depends?

A. Yes.

MR. KRAUSE: If we could please show PDX 4.4.

BY MR. KRAUSE:

Q. What types of patients does claim 1 and, by dependency, claim 11 require that the drugs be administered to?
A. Prostate cancer patients.
Q. And what is the relationship between mCRPC and prostate cancer?
A. mCRPC is a form or sub-type of prostate cancer, it is prostate cancer.
Q. Let's say a person administers therapeutically effective amounts of abiraterone acetate and prednisone to patients with mCRPC, is anything else required to directly infringe claim 1?
A. No.
Q. What does claim 11 say about therapeutically effective amounts of abiraterone acetate and prednisone?
A. It calls out the specific dosages of both compounds, 1000 milligrams per day of abiraterone acetate and 10 milligrams per day of prednisone.
Q. If those dosages are administered to a patient with mCRPC, what does claim 11 say about whether those amounts are therapeutically effective?
A. That they are, indeed, therapeutically effective.
Q. If the 1000 milligrams per day of abiraterone acetate and 10 milligram per day of prednisone are administered to a patient with mCRPC, are any other requirements in claim 11 that need to be found?
A. No.

Q. Now, let's look briefly at claims 4 and 8.

Have you prepared a demonstrative showing claims 4 and 8 and the claims from which they depend?

A. Yes.

MR. KRAUSE: Let's look at PDX 4.5.

BY MR. KRAUSE:

Q. What do claims 4 and 8 say about therapeutically-effective doses of abiraterone acetate and prednisone?

A. So claims 4 and 8 are, respectively, calling out the individual drugs.

So in claim 4, it's identifying the dose of abiraterone acetate as 1000 milligrams per day. And in claim 8, it's calling out the specific doses of prednisone that's therapeutically effective as 10 milligrams per day.

Q. Finally, let's look at claims 19 and 20. Have you prepared a demonstrative of claims 19 and 20 and the claims from which they depend?

A. Yes.

MR. KRAUSE: Let's look at PDX 4.6.

BY MR. KRAUSE:

Q. What do claims 19 and 20 say about therapeutically effective doses of abiraterone acetate and prednisone?

A. So claim 19 is dependent on claim 18 which is dependent on claim 12. So what it's doing it's identifying abiraterone -- the specific and therapeutically effective doses of abiraterone

acetate and prednisone for prostate cancer that is refractory, a refractory prostate cancer.

In claim 20, is building on that, and it's, again, calling out the specific dosages of abiraterone acetate and prednisone that are therapeutically effective when administered to patients that have had Docetaxel shown in claim 17, upon which claim 20 is dependent.

Q. Please turn to PTX-406 in your binder, if you would?

A. Got it.

Q. Do you recognize PTX-406 as a copy of the February 2018 Zytiga label?

A. I do.

Q. How do physicians, such as yourselves, use the Zytiga label?

A. First and foremost, what one does as a physician is, you look at why you would use a therapy and you look at the indications and usage, and that is where you start. Why would you use this therapy.

The rest of the document is then reviewed because that tells you some of the specifics on how to use the -- the --the -- the therapy in question here, Zytiga and prednisone. What doses is an example, certain warnings and precautions and specific issues that are related to that therapy.

Q. Did you analyze defendants' ANDA labels and the Zytiga label as part of your work in this case?

A. I did.
Q. Let's quickly identify the defendants' labels for the records. Is JTX-8011 Amerigen's label?
A. It is.
Q. Is PTX-359?
A. Got it.
Q. Is Amneal's label?
A. Yes.
Q. Is PTX-367 DRL's label?
A. Yes.
Q. Is PTX-372 Mylan's label?
A. Yes.
Q. Is PTX-383 Teva's label?
A. Yes.
Q. PTX-393, is that West-Ward's label?
A. Yes.
Q. And finally, is PTX-397 Wockhardt's label?
A. Yes.
Q. From whose perspective or expertise did you analyze defendants' ANDA labels and the Zytiga label?
A. A person of ordinary skill.
Q. At a high level, how do defendants' labels, ANDA labels, compare with the Zytiga label?
A. They're essentially the same, no substantial differences.
Q. How do the defendants' ANDA labels compare to one another?

A. The same answer.
Q. How would the defendants' use of abiraterone acetate differ if they follow defendants' ANDA labels instead of the Zytiga label for mCRPC patients?
A. They wouldn't differ.
Q. Let's look at Amneal's ANDA label as an example of defendants' ANDA labels.
Please turn to PTX-359.
A. Got it.
Q. The top of the first page has the heading "Highlights of Prescribing Information."
What does that mean?
A. That's the summary of the prescribing information. It's not as complete as the full prescribing information, which comes next.
Q. Okay. You anticipated my next question.
Please look at the bottom of the same page. It has the heading "Full Prescribing Information." What does that refer to?
A. As I just said, that's a more detailed description of the therapy. It's more robust, more detailed.
Q. Did you prepare a demonstrative showing the indications and usage section of the Amneal label?
A. Yes.
MR. KRAUSE: If we could, please display PDX 4.7.

BY MR. KRAUSE:
Q. What is shown here?
A. So you're seeing the indications and usage section for the highlights and -- of the prescribing information, and the full prescribing information.
Q. How do physicians use the indications and usage section of drug labels?
A. They go to it, generally, first to determine why a therapy is being used.
Q. What does the indications and usage section of Amneal's ANDA label tell physicians about how abiraterone acetate should be used?
A. That is to be used with prednisone for its treatment of patients with mCRPC.
Q. How does the indications and usage section of Amneal's label substantively compare to the other defendants' labels?
A. The same.
Q. How does a physician identify the appropriate dosage of the drug?
A. The next section is called the dosage and administration section, and that tells you what the dosage of the appropriate drugs are.
Q. Did you prepare a demonstrative showing the dosage and administration section of the Amneal label?
A. Yes.

MR. KRAUSE: Let's please display PDX 4.8.

BY MR. KRAUSE:

Q. And what is shown here?

A. You have the dosage and administration sections of the highlights of the prescribing information and full prescribing information.

Q. What does the dosage and administration section of Amneal's ANDA label instruct as to doses of abiraterone acetate and prednisone?

A. The dosage and administration section for mCRPC of abiraterone acetate is a thousand milligrams, and for prednisone it's 10 milligrams a day, it's 5 milligrams twice per day.

Q. How does the dosage and administration section of Amneal's label substantively compare to the other defendants' labels?

A. The same.

Q. Did you compare the asserted claims to the defendants' ANDA labels?

A. Yes.

Q. How does the method of treatment covered by the asserted claims compare to the method of treatment described in defendants' ANDA labels?

A. It's covered.

Q. Did you analyze whether following the instructions in defendants' ANDA labels would result in direct infringement of

the asserted claims?
A. Yes.
Q. What is your opinion as to whether someone following defendants' ANDA labels would directly infringe the asserted claims of the '438 patent?
A. That they would directly infringe.
Q. If you could, please turn to PTX-450 through 457 in your book.
A. Okay. I'm at 450.
Q. Generally, what are these exhibits?
A. These are exhibits showing a chart of the '438 patent claims against the defendants' proposed ANDA labels.
Q. For the record, let's identify which exhibit corresponds to which defendant. Is PTX-450 a comparison of the asserted claims to Amerigen's label?
A. Yes.
Q. And is PTX-451 a comparison of the asserted claims to Amneal's label?
A. Yes.
Q. Is PTX-452 a comparison of the asserted claims to DRL's label?
A. Yes.
Q. Is PTX-453 a comparison of the asserted claims to Mylan's labels?
A. Yes.

Q. Is PTX-454 a comparison of the asserted claims to Teva's label?
A. Yes.
Q. Is PTX-455 a comparison of the asserted claims to West-Ward's label?
A. Yes.
Q. Is PTX-456 a comparison of the asserted claims to Wockhardt's label?
A. Yes.
Q. And finally, is PTX-457 a comparison of the asserted claims to Zytiga's label?
A. Yes.
Q. What sections of the labels do the summary exhibits primarily refer to?
A. Dominantly, the indications and usage sections, the clinical trials section, and the dosage and administration section.
Q. How similar are the indications and usage sections and the dosage and administrations sections of defendants' ANDA labels and the Zytiga label, with respect to mCRPC?
A. There are no substantive differences.
Q. How did your analysis in the summary exhibit related to Amneal's ANDA label, PTX-451, compare to your analysis in the other summary exhibits of the other defendants' ANDA labels?
A. They are the same.

Q. Can we use Amneal's label as a representative example then?
A. Yes.
Q. Did you prepare a series of demonstratives to help explain your infringement analysis of each claim?
A. Yes.
Q. Are the demonstratives that you prepared labelled PDX 4.10 through PDX 4.53?
A. Yes.
Q. Let's take the asserted claims one at a time, starting with claim 11.
MR. KRAUSE: If we could please show PDX 4.10.
BY MR. KRAUSE:
Q. What claims does claim 11 depend upon?
A. Claim 11 depends on claim 10, which, in turn, depends on claim 1.
Q. Let's look at how claim 1 relates to defendants' ANDA labels first.
MR. KRAUSE: If we could show PDX 4.11.
BY MR. KRAUSE:
Q. Where is the claim element, "a method for the treatment of a prostate cancer in a human comprising," found in defendants' ANDA labels?
A. That is in the indications and usage section of the full prescribing information as shown here, where it calls out

metastatic castration-resistant prostate cancer in patients, and metastatic castration-resistant prostate cancer is a form of prostate cancer in a human being.

MR. KRAUSE: If we could please show PDX 4.12.

BY MR. KRAUSE:

Q. Where are the claim elements, "administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically-acceptable salt thereof, and a therapeutically effective amount of prednisone" found in defendants' ANDA labels?

A. Dosage and administration section of the full prescribing information, with a specific dosage of abiraterone acetate at 1000 milligrams a day and prednisone of 5 milligrams orally twice per day, or 10 milligrams total per day are called out.

Q. And again, the indications and usage section is referring to the use of abiraterone acetate and prednisone; is that right?

A. Yes, that's correct.

Q. How many elements of claim 1 are present when defendants' ANDA products are used, according to defendants' ANDA labels?

A. All of them.

Q. Let's look at claim 10 upon which claim 11 also depends.

MR. KRAUSE: If we could please show PDX 4.13.

BY MR. KRAUSE:

Q. Where is claim 10's claim element, "the method of claim 1

comprising" in defendants' ANDA labels?
A. In my previous discussion for claim 1.
MR. KRAUSE: If we could now show PDX 4.14.
BY MR. KRAUSE:
Q. Where is claim 10's claim element "administering to said human about 500 milligrams per day to about 1500 milligrams per day of abiraterone acetate or a pharmaceutically-acceptable salt thereof, and about 0.01 milligrams per day to about 500 milligrams per day of prednisone" in defendants' ANDA labels?
A. The dosage and administration section, the full prescribing information, which again calls out the specific doses of abiraterone acetate and prednisone as 1000 milligrams per day and 10 milligrams total per day, respectively. Those are dosages that fall within the range that are cited in claim 10.
Q. How many elements of claim 10 are present when defendants' ANDA products are used according to defendants' ANDA labels?
A. All.
Q. Now let's talk about claim 11 itself.
MR. KRAUSE: If we could please show PDX 4.15.
BY MR. KRAUSE:
Q. Where is claim 11's element "the method of claim 10 comprising" in defendants' ANDA labels?
A. In my discussion of claim 10.
Q. The one that you just provided?

A. Yes, the one that I just provided.

MR. KRAUSE: If we could please show PDX 4.16.

BY MR. KRAUSE:

Q. Where is claim 11's claim element "administering to said human about 1000 milligrams per day of abiraterone acetate or a pharmaceutically-acceptable salt thereof, and about 10 milligrams per day of prednisone" in defendants' ANDA labels?

A. Again, in the dosage and administration section of the full prescribing information where it describes the specific doses of abiraterone acetate and prednisone at a thousand milligrams per day and 10 milligrams per day total, respectively. And those dosages match precisely with those that are described in claim 11.

MR. KRAUSE: If we could please show PDX 4.17.

BY MR. KRAUSE:

Q. So how many elements of claim 11 are present when defendants' ANDA products are used according to defendants' ANDA labels?

A. All of them.

Q. Now let's talk about claim 4.

MR. KRAUSE: And if we could please show PDX 4.18.

BY MR. KRAUSE:

Q. What claims are claim 4 dependent upon?

A. Claim 4 is dependent on claim 3, which in turn is

dependent on claim 2, which in turn is dependent on claim 1.
Q. We've already covered claim 1, so let's look at claim 2.
MR. KRAUSE: Please show PDX 4.19.
BY MR. KRAUSE:
Q. Where is claim 2's claim element "the method of claim 1 wherein," in defendants' ANDA labels?
A. That was in my earlier discussion of claim 1.
MR. KRAUSE: If we could show PDX 4.20.
BY MR. KRAUSE:
Q. Where is claim 2's claim element, "the therapeutically effective amount of the abiraterone acetate, or pharmaceutically-acceptable salt thereof, is from about 50 milligrams per day to about 2,000 milligrams per day" in defendants' ANDA labels?
A. In the dosage and administration section of the full prescribing information, where the dosages of abiraterone acetate and prednisone are identified as 1000 milligrams and 10 milligrams total per day, respectively. I'm sorry, just abiraterone acetate is called out in the claim 2. So abiraterone acetate at 1000 milligrams per day, and that falls within the range that is identified in claim 2.
Q. How many elements of claim 2 are present when defendants' ANDA products are used according to the defendants' ANDA labels?
A. All.

Q. Now let's look at claim 3 upon which claim 4 also depends.

MR. KRAUSE: If we could show PDX 4.21.

BY MR. KRAUSE:

Q. Where is claim 3's claim element "the method of claim 2 wherein" in defendants' ANDA labels?

A. As you can see my immediate past discussion for claim 2.

MR. KRAUSE: If we could show PDX 4.22.

BY MR. KRAUSE:

Q. Where is claim 3's claim element, "the therapeutically effective amount of the abiraterone acetate, or a pharmaceutically-acceptable salt thereof, is from about 500 milligrams per day to about 1500 milligrams per day" in defendants' ANDA labels?

A. In the dosage and administration section of the full prescribing information, where the dosage of abiraterone acetate tablets are identified as a thousand milligrams per day, which is the doses that falls within the range described in claim 3.

Q. How many elements of claim 3 are present when defendants' ANDA labels are used according to defendants' -- defendants' ANDA products are used according to their labels?

A. All.

Q. Now let's look at claim 4 itself.

MR. KRAUSE: If we could show PDX 4.23.

BY MR. KRAUSE:

Q. Where is claim 4's claim element, "the method of claim 3 wherein," in defendants' ANDA labels?
A. See my discussion of claim 3 we just had.
MR. KRAUSE: If we could show PDX 4.24.
BY MR. KRAUSE:
Q. Where is claim 4's claim element, "the therapeutically effective amount of the abiraterone acetate, or pharmaceutically acceptable salt thereof, is about 1000 milligrams per day" in defendants' ANDA labels?
A. In the dosage and administration section of the full prescribing information. Again, abiraterone acetate tablets have a dosage that is identified as 1000 milligrams per day, and that precisely matches the dosage that's identified in claim 4.
MR. KRAUSE: If we could show PDX 4.25.
BY MR. KRAUSE:
Q. How many elements of claim 4 are present when defendants' ANDA products are used according to defendants' ANDA labels?
A. All.
Q. Now let's talk about claim 8.
MR. KRAUSE: If we could please show PDX 4.26.
BY MR. KRAUSE:
Q. What claims are claim 8 dependent upon?
A. Claim 8 is dependent on claim 7, which is, in turn, dependent on claim 6, which is, in turn, dependent on claim 1.

Q. We've already covered claim 1, so let's look at claim 6.

MR. KRAUSE: If we could please show PDX 4.27.

BY MR. KRAUSE:

Q. Where is claim 6's claim element, "the method of claim 1 wherein," in defendants' ANDA labels?

A. In my previous discussion for claim 1.

MR. KRAUSE: And if we could show PDX 4.28.

BY MR. KRAUSE:

Q. Where is claim 6's claim element "the therapeutically effective amount of the prednisone is from about 0.01 milligrams per day to about 500 milligrams per day" in defendants' ANDA labels?

A. It's also in the dosage and administration section of the full prescribing information which identifies the precise dosage of prednisone as 5 milligrams orally twice daily for a total of 10 milligrams per day, which falls within the range identified in claim 6.

Q. So how many elements of claim 6 are present when defendants' ANDA products are used according to defendants' ANDA labels?

A. All.

Q. Now let's look at claim 7 on which claim 8 also depends.

MR. KRAUSE: If we could show PDX 4.29.

BY MR. KRAUSE:

Q. Where is claim 7's claim element, "the method of claim 6

wherein," in defendants' ANDA labels?
A. In my discussion for claim 6.
MR. KRAUSE: If we could show PDX 4.30.
BY MR. KRAUSE:
Q. Where is claim 7's claim element, "the therapeutically effective amount of the prednisone is from about 10 milligrams per day to about 250 milligrams per day," in defendants' ANDA labels?
A. In the dosage and administration section of the full prescribing information, which identifies a dosage of prednisone of 5 milligrams orally twice daily or a total of 10 milligrams per day, which falls within the range that is described in claim 7.
Q. So how many elements of claim 7 are present when defendants' ANDA products are used according to defendants' ANDA labels?
A. All.
Q. Now let's look at claim 8 itself.
MR. KRAUSE: Please show PDX 4.31.
BY MR. KRAUSE:
Q. Where is claim 8's claim element "the method of claim 7 wherein," in defendants' ANDA labels?
A. In my discussion for claim 7.
MR. KRAUSE: If we could show PDX 4.32.
BY MR. KRAUSE:

Q. Where is claim 8's claim element, "the therapeutically effective amount of the prednisone is about 10 milligrams per day" in defendants' ANDA labels?
A. Dosage and administration section of the full prescribing information, which identifies a dosage of prednisone of 5 milligrams orally twice daily or 10 milligrams total per day, which precisely matches the dosage that's identified in claim 8.
MR. KRAUSE: If we could show PDX 4.33.
BY MR. KRAUSE:
Q. How many elements of claim 8 are present when defendants' ANDA products are used according to defendants' ANDA labels?
A. All.
Q. Moving along to claim 19.
MR. KRAUSE: If we could show PDX 4.34.
BY MR. KRAUSE:
Q. What claims are claim 19 dependent upon?
A. Claim 19 is dependent on claim 8, which in turn is dependent on claim 12, which in turn is dependent on claim 1.
Q. I'm sorry, Doctor, I believe you said claim 8?
A. I'm sorry. I misspoke. 19 is dependent on claim 18, which is in turn dependent on claim 12, which in turn is dependent on claim 1.
Q. We've already covered claim 1, so let's look at claim 12.
Do you see the element of claim 12 that says, "said

prostate cancer is refractory prostate cancer"?
A. Yes.
Q. Is it your understanding that the parties agreed on the meaning of the term "refractory prostate cancer"?
A. Yes.
Q. Did you prepare a demonstrative setting forth the agreed-upon definition of refractory prostate cancer?
A. Yes.
MR. KRAUSE: If we could, please, show PDX 4.35.
BY MR. KRAUSE:
Q. What is that agreed upon definition, Doctor?
A. Prostate cancer that is not responding to an anti-cancer treatment or prostate cancer that is not responding sufficiently to an anti-cancer treatment. Refractory prostate cancer can, also, include recurring or relapsing prostate cancer.
Q. Doctor, how does mCRPC relate to refractory prostate cancer, as that term has been defined?
A. It is a form or type of refractory prostate cancer.
Q. Let's turn back to claim 12.
MR. KRAUSE: If we could show PDX 4.36.
Q. Where is claim 12's claim element, "the method of claim 1 wherein," in defendants' ANDA labels?
A. In my discussion in support for claim 1.
MR. KRAUSE: If we could show PDX 4.37.

BY MR. KRAUSE:
Q. Where is claim 12's claim element, "said prostate cancer is refractory prostate cancer," found in the defendants' ANDA labels?
A. In the indications and usage section of the full-prescribing information, which identifies metastatic castration-resistant prostate cancer as the form of prostate cancer that is refractory, and refractory prostate cancer is what is described in claim 12.
Q. How many elements of claim 12 are present when defendants' ANDA products are used according to the defendant's ANDA labels?
A. All.
Q. Now, let's look on claim 18, on which claim 12 depends.
MR. KRAUSE: Please show PDX 4.38.
BY MR. KRAUSE:
Q. Where is claim 18's claim element, "the method of claim 12 comprising," in defendant's ANDA labels?
A. In my discussion for the support for claim 12.
MR. KRAUSE: If we could show PDX 4.39.
BY MR. KRAUSE:
Q. Where is claim 18's claim element, "administering to said human about 500 milligrams per day to about 1500 milligrams per day of abiraterone acetate, or a pharmaceutically acceptable salt thereof, and about 0.01 milligrams per day to about

500 milligrams per day of prednisone."

A. In the dosage and administration section of the full-prescribing information, with the dosage of abiraterone acetate is identified as 1000 milligrams per day and the dosage of prednisone is 5 milligrams orally twice daily or 10 milligrams total per day, and both of those dosages falls within the respective ranges that are identified in claim 8 -- 18, excuse me.

Q. So how many elements of claim 18 are present when the defendants' ANDA products are used according to the defendants' ANDA labels?

A. All.

Q. Now, let's look at claim 19 itself.

MR. KRAUSE: If we could show PDX 4.40.

BY MR. KRAUSE:

Q. Where is claim 19's claim element, "the method of claim 18 comprising," in defendants' ANDA labels?

A. In my discussion for the support for claim 18.

MR. KRAUSE: And if we could turn to PDX 4.41.

BY MR. KRAUSE:

Q. Where is claim 19's claim element, "administering to said human about 1000 milligrams per day of abiraterone acetate, or a pharmaceutically acceptable salt thereof, and about 10 milligrams per day of prednisone," in defendants' ANDA labels?

A. That's in the dosage and administration section of the full-prescribing information. It, again, calls out the dosages of abiraterone acetate at 1000 milligrams per day and prednisone at 5 milligrams orally twice daily for a total of 10 milligrams a day which match -- which are dosages that match precisely with those that are identified in claim 19.

MR. KRAUSE: If we could, please, show PDX 4.42.

Q. So how many elements of claim 19 are present when defendants' ANDA products are used according to the defendants' ANDA labels?

A. All.

Q. Now, let's look at the final asserted claim, claim 20.

MR. KRAUSE: If we could show PDX 4.43.

Q. What claims are claim 20 dependent upon?

A. Claim 20 is dependent on claim 17, which, in turn, is dependent on claim 14, which, in turn, is dependent on claim 13, which, in turn, is dependent on claim 12, which, in turn, is dependent on claim 1.

Q. We've already covered claims 1 and 12. So let's look at claim 13.

MR. KRAUSE: If we could show PDX 4.44.

BY MR. KRAUSE:

Q. Where is claim 13's claim element, "the method of claim 12 wherein," in defendants' ANDA labels?

A. In my previous discussion for the support for claim 12.

MR. KRAUSE: Now, if we could turn to PDX 4.45.

BY MR. KRAUSE:

Q. Where is claim 13's claim element, "the refractory prostate cancer is not responding to at least one anti-cancer agent," found in defendants' ANDA labels?

A. In the indications and usage section of the full-prescribing information and the clinical study section for the -- of the full-prescribing information.

Q. Does the indications and usage section of defendants' ANDA labels encompass mCRPC patients who are not responding to docetaxel?

A. Yes. The indications and usage section describe metastatic castration-resistant prostate cancer, and a subset of those patients may have had docetaxel. So docetaxel-treated mCRPC patients represent a subset of all mCRPC patients.

Q. Where do defendants' ANDA labels specifically refer to treatment of docetaxel refractory prostate cancer patients?

A. So that's in the clinical study section of the full prescribing information, where the clinical trial Cougar AA301 -- the 301 study -- was conducted in patients with metastatic CRPC who had received prior docetaxel chemotherapy.

Q. What does the label's statement in the clinical studies section, "patients with metastatic CRPC who had received prior docetaxel chemotherapy," refer to?

A. Those are patients who have metastatic

castration-resistant prostate cancer and have, also, received docetaxel-based chemotherapy.

Q. What does the label's statement in this section, "70 percent of patients had radiographic evidence of disease progression, and 30 percent had PSA-only progression," meaning with respect to whether patients in the trial had received docetaxel?

A. Those numbers are, specifically, calling out the manner in which the cancer progressed or got worse after docetaxel-based chemotherapy.

Q. Will defendants' ANDA products be used with prednisone for mCRPC who are not responding to the anti-cancer agent, docetaxel?

A. Yes.

Q. How many elements of claim 13 are present when defendants' ANDA products are used according to their labels for mCRPC who are not responding to the anti-cancer agent, docetaxel?

A. All.

Q. Now, let's look at claims 14 and 17, on which claim 20 depends.

MR. KRAUSE: Please show PDX 4.46.

BY MR. KRAUSE:

Q. Where is claim 14's claim element, "the method of claim 13," in defendants' ANDA labels?

A. In my discussion for the support for claim 13.

MR. KRAUSE: If we could show PDX 4.47.

BY MR. KRAUSE:

Q. Where is claim 14's claim element, "the at least one anti-cancer agent comprises a hormonal ablation agent, an anti-androgen agent or an anti-neoplastic agent," in defendants' ANDA labels?

A. In the indications and usage section of the full-prescribing information and the clinical studies section of the full-prescribing information.

Q. Is docetaxel an anti-neoplastic agent?

A. Yes.

Q. How many elements of claim 14 are present when defendants' ANDA products are used according to their labels for mCRPC patients who are not responding to the anti-cancer agent, docetaxel?

A. All.

Q. Let's look at claim 17.

MR. KRAUSE: And if we could show PDX 4.48.

BY MR. KRAUSE:

Q. Where is claim 17's claim element, "the method of claim 14 wherein," in defendants' ANDA labels?

A. In my discussion for the support for claim 14.

MR. KRAUSE: If we could show PDX 4.49.

BY MR. KRAUSE:

Q. Where is claim 17's claim element, "the anti-neoplastic

agent comprises docetaxel," in defendants' ANDA labels?
A. In the indications and usage section of the full-prescribing information where the patients are described as metastatic castration-resistant prostate cancer which can include, but is not limited to, patients who have had docetaxel-based chemotherapy; as well as the clinical studies section of the full-prescribing information, where the 301 study is, specifically, described. A study which was conducted in patients who had received prior docetaxel chemotherapy.
Q. How many elements of claim 17 are present when defendants' ANDA products are used according to their labels for mCRPC patients who are not responding to the anti-cancer agent, docetaxel?
A. All.
Q. Finally, let's look at claim 20 itself.
THE COURT: By the way, just to satisfy my curiosity, is docetaxel a form of what I may be familiar with as Taxol?
THE WITNESS: No. Not quite, close. So Taxol or Paclitaxel?
THE COURT: Yes.
THE WITNESS: Is the parent compound in docetaxel. Is a semi-synthetic derivative. Docetaxel is, also, called Taxotere. That's the brand name for docetaxel.
Docetaxel is the brand name for Taxotere, T-a-x-o-t-e-r-e.

I'm sorry, I misstated that. Docetaxel is the chemical or generic name for the brand name, Taxotere.

BY MR. KRAUSE:

Q. So if we could turn to claim 20 itself.

MR. KRAUSE: And, please, show PDX 4.50.

BY MR. KRAUSE:

Q. Where is claim 20's claim element, "the method of claim 17 comprising," in defendants' ANDA labels?

A. In my discussion for the support for claim 17.

MR. KRAUSE: If we could show PDX 4.51.

BY MR. KRAUSE:

Q. Where is claim 20's claim element, "administering to said human about 1000 milligrams per day of abiraterone acetate, or a pharmaceutically-acceptable salt thereof, and about 10 milligrams per day of prednisone," in defendants' ANDA labels?

A. In the dosage and administration section of the full-prescribing information where the dosage of abiraterone acetate is 1000 milligrams once per day and the dosage of prednisone is 5 milligrams orally twice daily for a total of 10 milligrams per day, which are the dosages that precisely match with the dosages of those drugs described in claim 20.

MR. KRAUSE: If we could please show PDX 4.52.

BY MR. KRAUSE:

Q. So how many elements of claim 20 are present when

defendants ANDA products are used according to their labels for mCRPC patients who are not responding to the anti-cancer agent, docetaxel?

A. All.

Q. Just so we are clear, do all of the defendants' labels contain, substantively, the same instructions as the Amneal label we just walked through?

A. Yes.

Q. Is the same infringement analysis we just went through applicable to each of the defendants' labels?

A. Yes.

MR. KRAUSE: If we could show PDX 4.53.

BY MR. KRAUSE:

Q. In summary, are all elements of the asserted claims met by following the instructions on defendants' ANDA labels?

A. Yes.

Q. Does the Zytiga label contain, essentially, the same instructions we just discussed in relation to the defendants' ANDA labels?

A. Yes.

Q. Are all elements of the asserted claims, likewise, met by following the instructions of the Zytiga label?

A. Yes.

Q. We've run through the asserted claims. Defendants, in their pretrial brief, also contend that plaintiffs must prove

that prednisone, when administered with defendants' abiraterone products, has anti-cancer effects.

Do you have an opinion on whether prednisone has an anti-cancer effect when administered with defendants' abiraterone products, according to their labels?

A. Yes, my opinion is that prednisone, unequivocally, has an anti-cancer effect, when administered with abiraterone acetate, for the treatment of mCRPC patients.

Q. We will cover that in more detail later.

In your experience, how common is it for physicians to follow the Zytiga label?

A. Very common.

Q. And how common is it for physicians to prescribe abiraterone acetate with prednisone?

A. Extremely common.

Q. Do you prescribe abiraterone acetate with prednisone to your mCRPC patients?

A. Yes.

Q. How often do you prescribe abiraterone acetate with prednisone?

A. Always.

Q. In your experience, why do physicians with mCRPC patients use abiraterone acetate with prednisone?

A. Because of its treatment effect on mCRPC patients, specifically, it makes them live longer.

Q. How do physicians actually write prescriptions for abiraterone acetate and prednisone?

A. Two separate prescriptions, if you will, have to be written.

In general, the abiraterone acetate prescription is not a simple prescription because it comes from a specialty pharmacy, and the drug has to get prior authorization from the patient's insurance if they're, not say, for example, a veteran. But in most practices, two sep -- a prescription is sent in that is separate for abiraterone acetate and a separate prescription for prednisone.

Q. Generally speaking, what types of instructions do physicians give their patients when prescribing abiraterone acetate with prednisone?

A. A number of instructions. They describe how to take the drug. So, for example, do you take a drug on an empty stomach, with food, what happens if you miss a dose, do you catch up the same day, can you catch up the next day, what are some of the side effects that one might have to watch out for.

And, usually, I tell patients to contact me if they have any questions. And they can contact me by any one of multiple mechanisms; they have my personal email, they have my office number, and they have the UCLA page operator.

Q. What do physicians use as the basis for their instructions to patients about how to take Zytiga plus prednisone?

A. That they should be taken together, not literally at the same time, but always together. And that the Zytiga is taken on an empty stomach, specifically, either one hour prior to meals or two hours after a meal, so it has to be taken on an empty stomach. And the prednisone is taken twice per day, 5 milligrams twice per day, with food, typically breakfast and dinner.

Q. And what role does the label play in the instructions that physicians give their patients?

A. It informs the physicians on these instructions that I just detailed.

Q. Do you expect patients to follow their physicians' instructions?

A. Yes.

Q. What happens if a physician learns that a patient is not taking Zytiga plus prednisone as prescribed?

A. It depends. If it's a patient who is just not compliant and recalcitrant to encouragement, then I would discontinue the therapy and look for an alternative.

If a patient says, oh, I forgot to get the refill, but continued wanting to take it, this is an example, I would likely continue that therapy. But it really depends on the individual case.

Q. Do you expect physicians to prescribe defendants' ANDA products in the same way that you prescribe Zytiga?

A. Yes.
Q. And why is that?
A. Because the defendants' proposed ANDA label -- labels, are essentially identical to that of the Zytiga label, so they are instructing the same thing.
Q. Are all elements of the asserted claims met when defendants' labels are followed?
A. Yes.
Q. And do the instructions on defendants' labels encourage direct infringement of the asserted claims?
A. Yes, that's my opinion.
Q. Have you analyzed whether the defendants will induce infringement of the asserted claims?
A. Yes.
Q. And what did you conclude?
A. That they do induce infringement.
Q. Did you prepare a demonstrative to help explain your analysis of induced infringement?
A. Yes.
MR. KRAUSE: If we could please show PDX 4.54.
THE COURT: Looking ahead, when you complete this induced infringement demonstrative, I'd like to take our morning break. Okay?
MR. KRAUSE: Yes, Your Honor.
BY MR. KRAUSE:

Q. What did you conclude as to whether defendants' have knowledge of the '438 patent?
A. That they do have knowledge of the '438 patent.
Q. And what is your basis for that?
A. Well, one is the fact that we're here today, okay. Two, is that when they submit their ANDA, there's something called a Paragraph 4 certification, which establishes that they have looked, are aware of the patents that are associated with the product at hand, with Zytiga.

So that's the evidence that I have.

Q. What did you conclude as to whether there will be direct infringement if defendants' ANDAs are approved?
A. That there would be direct infringement. And that is based on the fact that physicians would follow the directions in the ANDA -- the defendants' ANDA labels. And those directions cover all of the elements of all of the claims that are asserted in the '438 patent.
Q. What evidence are you aware of that defendants will knowingly induce infringement with specific intent?
A. The defendants' encourage infringement by distributing abiraterone acetate with the label that instructs the direct infringement. As I said, they already -- they know of the infringement by the Zytiga orange book listing, as I mentioned, and their knowledge of the patent claims.

They also -- the defendants, that is, know that the

patent claims identify the specific dosages of 1000 milligrams per day of abiraterone acetate and 10 milligrams per day of prednisone as the therapeutically effective amount.

In addition, if the Court rules that following the defendants' labels results in direct infringement, that would be indisputable evidence that defendants know and intend infringement.

Q. In sum, what is your opinion with respect to whether the defendants will induce infringement of the asserted claims?

A. They will induce infringement.

MR. KRAUSE: Your Honor.

THE COURT: Okay. Let's take our morning break, about 15 minutes. It's close to 10:50 now. Let's return at five past 11.

(Recess at 10:48 a.m. to 11:08 a.m.)

THE COURT: When you're ready.

MR. KRAUSE: Thank you, Your Honor.

BY MR. KRAUSE:

Q. Let's move to contributory infringement.

Have you analyzed whether defendants will contribute to the infringement of the asserted claims?

A. Yes.

Q. What did you conclude?

A. They will contributorily infringe.

Q. Did you prepare a demonstrative to illustrate how the

elements of contributory infringement are satisfied here?
A. Yes.
MR. KRAUSE: If we could put up PDX 4.55.
BY MR. KRAUSE:
Q. Let's take these elements one at a time. What evidence are you aware of that defendants had knowledge of the '438 patent?
A. It's my description earlier, one, that we're here today discussing the '438 patent, so that's inherently clear or obvious. Two, they had knowledge through their ANDA label submission or ANDA submission, rather. And that requires paragraph certification and knowledge that the patent was listed in the orange book.
Q. What evidence are you aware of that defendants will sell a component used to directly infringe the '438 patented methods?
A. Well, that's what they're seeking to do. They're seeking to distribute abiraterone acetate for its use as described in the '438 patent methods of treatment.
Q. Is defendants' generic abiraterone acetate a material part of the '438 patented invention?
A. Yeah. There's only two drugs in that patent. One of them is abiraterone acetate. So yes, it's a material component of the invention.
Q. In your view, did the defendants know that their ANDA products are especially made for an infringing use and not a

staple article suitable for substantial non-infringing use?
A. Yes, that's my understanding. They know that the use of their product will result in the direct infringement of the asserted claims. The defendants know this from their understanding of the claim language, and they cannot market their abiraterone acetate for uses that are not on the labels. And if the Court rules that following defendants' labels results in direct infringement, it is indisputable that defendants know products are especially made for infringement.
Q. Why do you believe defendants --
THE COURT: Hold on one second. Let me just ask you. Are you aware of any significant off-label use of this combination therapy?
THE WITNESS: No, sir.
THE COURT: You can put it under the short leg of a table if you want to, but I mean, any medical use to which this is commonly put?
THE WITNESS: Absolutely not, no such use.
THE COURT: All right. Go ahead.
BY MR. KRAUSE:
Q. Why do you believe defendants' ANDA products have no substantial non-infringing uses, with respect to Claims 4, 8 and 11, which are directed to prostate cancer?
A. As we said, the only indication in the label is for metastatic castration-resistant prostate cancer, which call out

a therapeutically effective amount of abiraterone acetate and prednisone at 1000 and 10 milligrams per day, which are the dosages that are cited in the claims as well as in the patent, so it's really the same concept, same patients, same dosages, same disease state.

Q. Why do you believe defendants' ANDA products have no substantial non-infringing uses with respect to claim 19, which is directed to refractory prostate cancer?

A. Because metastatic castration-resistant prostate cancer is a form of refractory prostate cancer.

Q. Finally, let's talk about claim 20, which is directed to refractory prostate cancer that is not responding to docetaxel. Could defendants' ANDA products be used with prednisone in mCRPC patients who haven't received docetaxel before?

A. Yes. That's indicated in the indications and usage sections, which covers mCRPC. A subset of those patients have not had docetaxel, and a subset may have had docetaxel.

Q. And why do you believe defendants' ANDA product have no substantial non-infringing uses with respect to the asserted claims when considering claim 20?

A. Because they will infringe other claims.

Q. In the pretrial brief, defendants argued that the use of abiraterone without prednisone is a substantial non-infringing use. Do defendants' labels recommend using abiraterone acetate with prednisone?

A. Yes, they always recommend abiraterone acetate with prednisone.
Q. Do they ever recommend using abiraterone acetate without prednisone?
A. No.
Q. How often do you prescribe abiraterone acetate to be administered without prednisone?
A. Never.
Q. To your knowledge, how often do physicians prescribe abiraterone acetate to be administered without prednisone?
A. Very, very uncommonly.
Q. What is your opinion as to whether administration of defendants' generic abiraterone acetate without prednisone is a substantial non-infringing use?
A. It's not. It's not in the label. It's not.
Q. So would that use be unusual and off-label?
A. That would be off-label, yes.
Q. Do defendants' labels recommend administering prednisone at a dose of less than 10 milligrams per day?
A. No.
Q. How often is abiraterone acetate administered to mCRPC patients with a dose of prednisone that is less than 10 milligrams per day?
A. Very, very uncommonly.
Q. What is your opinion as to whether administration of

defendants' generic abiraterone acetate, with a dose of prednisone that is less than 10 milligrams per day, is a substantial non-infringing use?

A. It is not a substantial non-infringing use, not an infringing use.

Q. Not a substantial --

A. It would be off-label.

Q. And why is that?

A. Because the label cites a specific dose for mCRPC of abiraterone acetate, 1000 milligrams and prednisone of 10 milligrams per day.

Q. Do defendants' labels recommend using abiraterone acetate with Eplerenone?

A. No.

Q. Just to review, what is Eplerenone?

A. So Eplerenone is a -- what's called a competitive antagonist of the mineralocorticoid receptor. So, essentially, what it does is it interferes with the ability of mineralocorticoids to bind its cognate receptor, to turn on its own receptor.

Q. Is it common to use Eplerenone instead of prednisone with abiraterone acetate?

A. No.

Q. Is using defendants' generic abiraterone acetate with Eplerenone a substantial non-infringing use?

A. No.
Q. I'd like to shift gears a bit, Doctor, and talk a little bit about your experience in speakers bureaus and so forth. Do you consult for pharmaceutical companies?
A. Yes.
Q. What companies do you consult for?
A. I recently consulted for Bayer, I think Astellas, Johnson & Johnson, and that's all I can think of that was recently.
Q. Why do you consult for pharmaceutical companies?
A. I'm asked to consult, and I choose to consult because I gain insight into drug development, I get insight into what's coming down the pipeline that I can tell patients. And, importantly, I can have input into drug development and also participate in drug development.
Q. Have you also served on speakers bureaus for pharmaceutical companies?
A. Yes.
Q. What companies have you served on speakers bureaus for?
A. In the distant past, Sanofi-Aventis, Medivation, and currently, Johnson & Johnson.
Q. Why do you participate in speakers bureaus?
A. I've been asked, and it allows me to speak to community physicians and healthcare providers and disseminate information that I think will be beneficial to patients. I do have some interest in community doctors knowing me and seeing me more and

more. That's a way of connecting to the community and having name and face recognition so that they can refer patients comfortably to me, especially for clinical trials.

Q. How long did you serve on Janssen's speakers bureau for Zytiga?

A. Somewhere around 2013 is when I started. I don't remember the exact date that it started.

Q. Are you still on that bureau?

A. I'm on the speakers bureau. The Zytiga speakers bureau was discontinued.

Q. What did you do as a member of Janssen's speakers bureau?

A. I presented FDA-approved material that provides a fair and balanced overview and discussion of Zytiga and prednisone, in combination, for mCRPC.

Q. On average, about how much were you compensated per year for your work as a member of Janssen's speakers bureau?

A. I would say on average, over that period of time, of about $30,000.

Q. Have you ever turned down an invitation to join a speakers bureau?

A. Yes, on more than one occasion. I just turned down an invitation from Pfizer.

Q. And why is that?

A. One of the principal reasons is, if I don't feel comfortable with the drug -- committed to the drug, and can't

speak to it in a genuine way.
Q. Let's turn to the defendants' non-infringement arguments. Defendants argued in the pretrial brief that they will not induce infringement because their labels contain no information directing physicians or patients to use prednisone as an anti-cancer agent.
Did you see any language in the asserted claims requiring any particular knowledge or intent?
A. No.
Q. Did you see any language in the asserted patent claims requiring that the person administering the drugs intend for prednisone to treat prostate cancer?
A. No.
Q. Did you see any language in the asserted patent claims requiring that the person administering the drugs know that prednisone contributes to anti-cancer effects in the combination?
A. No.
Q. What do defendants' ANDA labels tell physicians about the role of prednisone in combination with abiraterone acetate?
A. That it is contributing to the overall anti-cancer effect when used in combination with abiraterone acetate.
Q. What parts of defendants' ANDA labels did you primarily rely upon to reach that opinion?
A. The indications and usage section, predominantly, but also

the dosage and administration section and the clinical trials section.

Q. Let's start with the indications and usage section of defendants' ANDA labels, again using Amneal's ANDA label as a representative example.

Did you prepare the demonstrative showing the indications and usage section of Amneal's label?

A. Yes.

MR. KRAUSE: Let's look at PDX 4.56.

BY MR. KRAUSE:

Q. Remind us again, what do physicians use the indications and usage section for?

A. When you open up a label, the first thing your eye goes to and what it naturally does is, it goes to the indications and usage section to identify why you're going to use the therapy that's therein described.

Q. How do the indications and usage sections of defendants' ANDA labels compare to the Zytiga label, with respect to mCRPC?

A. The same.

Q. What would a physician understand abiraterone acetate and prednisone are used for based on the indications and usage section of defendants' ANDA labels?

A. They are to be used in combination for mCRPC.

Q. In combination with what?

A. With -- abiraterone acetate and prednisone are to be used

in combination for mCRPC.
Q. What else does the indications and usage section of defendants' ANDA labels suggest abiraterone acetate and prednisone are used for?
A. Nothing else.
Q. Is any disease or condition other than mCRPC mentioned in the indications and usage section of defendants' labels?
A. No.
Q. Does the indications and usage section say anything about using prednisone to treat side effects of abiraterone acetate?
A. No, for sure, but I would use a different word than "treat" when I use prednisone with respect to side effects because "treat" has a specific meaning in this context.
Q. Can you clarify that?
A. You asked me the question about whether or not prednisone is described in the indications and usage to treat side effects, and I just said "treat" has a specific meaning in this context as an anti-cancer effect. So I would just say manage side effects, or something like that.
Q. Okay. But regardless, the indications and usage section doesn't say anything about using prednisone or abiraterone acetate for side effects. Is that fair to say?
A. That's correct.
Q. The indications and usage section refers to "treatment of patients" with mCRPC. How would physicians interpret treatment

"of patients" compared to "treatment of the disease" in the context of a drug label?

A. They're the same.

Q. Are you familiar with Taxotere?

A. Yes, sir.

Q. What is Taxotere?

A. Taxotere is the brand name for docetaxel. Docetaxel is a cytotoxic chemotherapy drug, and it is a semisynthetic derivative from Paclitaxel, which is derived from the bark of the Pacific yew tree. And it is a chemotherapy drug that is used across oncology, including prostate cancer.

Q. Are you aware of a Taxotere label specifying that Taxotere, in combination with prednisone, is indicated for the treatment of patients with prostate cancer?

A. Yes.

Q. Is the structure of that Taxotere indication similar to the indications and usage for Zytiga?

A. Yes.

Q. What would that Taxotere indication mean if read in isolation?

A. If one looks at the labels in isolation without incorporating any other information, knowledge, experience, et cetera, it has the same meaning, in that Taxotere is approved in combination with prednisone to treat, I believe, the label uses hormone refractory or androgen-dependent, because it was

originally approved in 2004 before we started to use the terms "mCRPC." But effectively, the same disease in the same patients.

Q. What would that Taxotere indication mean to a physician or skilled person reading the label?

A. So when one looks at a label, one doesn't look at it in isolation. We do use our brains and we try to incorporate our knowledge, training, experience -- the peer-reviewed literature.

And with Taxotere, there's no rationale to combine Taxotere with prednisone for its anti-cancer effect. In other words, there's never a hypothesis proposed that I am aware of that ever suggested that prednisone could potentiate Taxotere's effect.

In addition, there's no clinical empiric evidence to support that concept. In other words, there was no analogous study that was done with Zytiga and prednisone when there were all of these Phase I and Phase II studies, which in my view, established the rationale for combining abiraterone acetate with prednisone.

Q. Let's talk about the dosage of administration section of defendants' ANDA label.

A. Sure.

Q. Did you prepare a demonstrative showing the dosage and administration section of Amneal's label?

A. Yes.

MR. KRAUSE: If we could please put up PDX 4.57.

BY MR. KRAUSE:

Q. Do you see the heading of Section 2.1 in Amneal's label entitled "Recommended Dose For Metastatic CRPC?"

A. Yes.

Q. What does the phase "recommended dose for metastatic CRPC", in the dosage and administration section, teach about the effect of prednisone with abiraterone acetate?

A. That it's being used to treat, with the doses cited, metastatic CRPC.

Q. What does the dosage and administration section of defendants' ANDA labels provide, with respect to recommended dosages of prednisone, for anything other than treating mCRPC, such as preventing abiraterone acetate side effects?

A. Nothing.

Q. The dosage and administration section of Amerigen, Mylan and Westward's labels omit the phrase "for metastatic CRPC."

What impact, if any, would that have on how physicians understand those defendants' labels, compared to the other defendants' labels?

A. It wouldn't impact. The dosage and administration we know refers directly back to the indications and uses section, so it would not impact.

Q. Let's look at the clinical studies' section of the

defendants' ANDA labels. Did you prepare a demonstrative showing portions of the clinical studies' section of Amneal's label?

A. Yes.

MR. KRAUSE: Let's look at PDX 4.58.

BY MR. KRAUSE:

Q. What does the clinical studies' section of the defendants' ANDA labels generally describe?

A. So in this example here, it's describing the efficacy and safety of abiraterone -- abiraterone acetate with prednisone in three randomized controlled international studies. I should say, this is inaccurate, because the defendants' ANDA labels only describe two of those controlled trials.

Q. So they don't describe the trials relating to mCSPC?

A. That's correct.

Q. They were carved out?

A. Right. So they -- in the indications, as we discussed, they carved out mCRPC and left out mCSPC because that's protected, currently, by the FDA. So there's no description of the clinical trial related to mCSPC in their labels.

Q. What was responsible for the anti-cancer efficacy of the 301 and 302 studies?

A. Abiraterone acetate and prednisone.

Q. Where does the clinical studies section refer to the efficacy of the combination?

A. It refers to it in the -- in these tables where they're describing the survival benefit in the two studies. So what they're doing here is they're describing median survival -- this is the 301 or post-chemotherapy study. They're also describing what's called a hazard ratio. So a hazard ratio of -- sorry about that -- a hazard ratio that's shown here, a hazard ratio of about .65, which means about a 35 percent reduction in the risk of dying for patients who got the abiraterone acetate with prednisone.

And then the P value. This is a statistical value that is describing the significant -- essentially, the way I read that, is that there's a one in 10,000 chance that those results occurred by chance. There's similar data described for the 302 study, which is the prechemotherapy study. So say, it's a quantitative summary of the results.

Q. In addition to those data, the first sentence of the section refers to the efficacy and safety of Zytiga with prednisone was established; is that right?

A. Yes, that's what we read.

Q. And, likewise, under the headings for 301 and 302, it refers to the improvement in overall survival for patients treated with Zytiga with prednisone; is that correct?

A. Correct.

Q. What can a physician conclude about the respective anti-cancer effects of abiraterone acetate and prednisone from

the data recited in the clinical studies section?
A. That abiraterone acetate and prednisone are contributing to the anti-cancer effect that's observed in these controlled trials.
Q. Could a physician conclude that the anti-cancer effects are attributable only to abiraterone acetate?
A. No, a physician would not make that conclusion.
Q. Do defendants' clinical studies section --
THE COURT: Expand on that a little bit. I suppose, ideally, we would have a third configuration in which prednisone would be replaced by a placebo and perhaps that would help in that conclusion, but explain to me what you mean.
THE WITNESS: Sure. So in the design of these clinical trials, the clinical trial protocols would -- were designed based upon earlier data. So the way it works, is that there's a hypothesis, so that was -- the de Bono hypothesis, regarding, one, how abiraterone acetate could influence adrenal hormones and he, also, predicted the mechanism of resistance and how prednisone or corticosteroids could reverse that resistance. And then that was tested, and then in that extension study, the 001 extension study, it was unequivocally established that that hypothesis was accurate. And it was followed up on phase II studies, that further confirmed the hypothesis. So the hypothesis was already established. So at the time that the randomized controlled trials were being

designed, there was really no need to add an extra arm. There was no need, because it would have subjected more patients to unnecessary research. It would have profoundly increased the number. It wouldn't just be adding the same number of patients because there's -- in another arm. My understanding is, as you increase the number of arms, because you do comparisons, that there may need to be even more patients per arm. So you're talking about cost, safety, et cetera.

So in my view, if you look at all the data together, the abiraterone acetate, in combination with prednisone, is really established to be the effective combination not either one on its own.

THE COURT: So are you saying that we cannot reach a conclusion just by looking at what's in front of me here on this slide, but it requires the context of the earlier studies?

THE WITNESS: Yeah. So, typically, what a physician would do would be, okay, there's the 301 study, let me pull that paper. And they look at the paper and they see descriptions of the hypothesis and references to the earlier phase studies to get a more fulsome assessment of what is going on.

So, yes, Your Honor, you're correct. If we look at the clinical studies' section purely in isolation, that one cannot make an unequivocal determination about the relative contribution of abiraterone and prednisone to the overall

effect.

THE COURT: Thank you.

BY MR. KRAUSE:

Q. What do you mean by "the relative contribution," Doctor?

A. The quantitative contribution percentage-wise. I don't think it really matters very much, they're both contributing.

Q. That, regardless, your view of those data is that those data indicate that both abiraterone acetate and prednisone are contributing in the anti-cancer effect?

A. Yes, absolutely. Those phase III studies were not done in isolation, in a black box, they were done in the context of previous data. So, yes, that's my conclusion.

Q. Do defendants' clinical studies' section, aside from those of the Amerigen label, contain the same information?

A. Yes.

Q. If you turn in your binder to JTX-8011, which is Amerigen's label.

A. Got it.

Q. And look at the page stamped 104. It's the "clinical studies" heading.

A. Okay.

Q. Amerigen's label refers to the efficacy and safety of abiraterone acetate tablets rather than abiraterone acetate tablets with prednisone, like the other labels. Do you see that?

A. Yes, I do. I do.
Q. And what is the revision date of the Amerigen label?
A. I believe this is 2015 -- or 20 --
Q. If you look at the last page.
A. Sorry. The very last page -- what page number is that?
THE COURT: Last page before the next --
THE WITNESS: I'm sorry. The original date is February 2015. So this is the label that is not yet updated to include abiraterone plus prednisone, that's my understanding.
Q. I believe that's said 3/2015, is that March rather than February, Doctor?
A. I'm sorry -- I'm looking at the wrong one here. This is JTX-8011?
Q. Yes, Doctor.
A. So on Page 109 it says "revision 2/2015." Should I be looking at something else?
Q. If you look at the very last page.
A. The very last page. Oh, yes. I'm sorry, yes, it says March 2015, yes.
Q. Why does this language exist in Amerigen's label and not the updated labels of the other defendants?
A. It's just what was in the old label. It hasn't been updated yet.
Q. Is the clinical studies' section of Amerigen's label otherwise essentially identical to the other defendants'

labels?
A. Yes.
Q. Would this difference, or other references in Amneal's label to abiraterone acetate that do not say "with prednisone", cause physicians to interpret Amerigen's label differently from that of the other defendants?
A. No.
Q. And why is that?
A. Because all of the material is essentially the same. All of the sections, the indications and usage section, all -- the dosage and administration, the clinical trial sections are all the same.
Q. And in Amerigen's old label, when it refers to "abiraterone acetate," how do you interpret that with respect to whether it encompasses prednisone?
A. It encompasses prednisone. It's a shorthand way of calling out that particular study arm.
Q. Let's turn next to the "warnings and precautions section." Why do physicians use a "warning and precautions section" on drug labels?
A. So what a physician does is he looks at the "indications and usage section" and once that decision is made to deliver therapy, or to consider delivering that therapy, one wants to know about issues that may come up when administering that therapy, abiraterone and prednisone. So this is describing

some warnings and precautions that we want to do to keep patients -- want to follow and be aware of in order to keep patients as safe as possible.

Q. How does the content of the "warnings and precautions section" impact the meaning of the "indications and usage"?

A. They're unrelated. It does not impact.

Q. Did you prepare a demonstrative showing section 5.2 of the "warnings and precautions" section of Amneal's label?

A. Yes.

MR. KRAUSE: Let's look at PDX 4.59.

BY MR. KRAUSE:

Q. Is section 5.2, essentially, the same in the other defendants' ANDA labels and the Zytiga label?

A. Yes.

Q. Is section 5.2 a warning about adrenal insufficiency?

A. Yes, that's what it's about.

Q. What creates the risk of adrenal insufficiency that's described here on the label?

A. Prednisone.

Q. Does section 5.2 of the defendants' ANDA labels suggest that abiraterone acetate causes adrenal insufficiency?

A. No.

Q. What is creating the risk of adrenal insufficiency when patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress?

A. So when corticosteroids like prednisone are administered from the outside, exogenously, the patient takes the corticosteroid as a pill, for example, the prednisone, for example. The adrenal glands see that and kind of go to sleep, if you will. So they stop making their own internal or indigenous corticosteroids and there are situations where a patient may need to make -- the adrenal glands need to make its own cortisol, those would be ones which you withdraw or taper the prednisone or -- and the adrenal glands need to make up for that loss -- or when patients undergo what we call a physiologic stress, a severe infection, a major trauma, a major surgery, that normally requires additional cortisol to respond to that stress. So if the patient is on prednisone, for example, and the adrenal gland is asleep, that additional cortisol would not -- or another group of corticoids would not be appropriately synthesized to manage that stressful situation.

Q. In the last sentence of the third paragraph of section 5.2 which we have here, the defendants' ANDA label states "increased doses of corticosteroids may be indicated before, during and after stressful situations." Why may increased doses of corticosteroids be indicated before, during and after stressful situations?

A. For the same reason that I just described, they need to make additional steroids in those particular contexts.

Q. How common is it for prednisone to be withdrawn or dose reduced?
A. In the context of abiraterone acetate? Or in general?
Q. In general, yes, Doctor.
A. So that would be, in my experience, uncommon. Very uncommon.
Q. Extremely rare?
A. Yeah.
Q. Do the defendants' labels recommend withdrawing or reducing the dose of prednisone?
A. No.
Q. Now turn to section 5.1 of the "warnings and precautions section" in the Amneal's ANDA label.
A. Okay.
Q. Did you prepare a demonstrative showing section 5.1 of that label?
A. Yes.
Q. Let's look at PDX 4.60.
A. Okay.
Q. What does this section of the label address?
A. This is addressing, in the "warnings and precautions," "hypertension, hypokinemia and fluid retention or edema due to mineralocorticoid excess."
Q. Is section 5.1 of Amneal's label, essentially, the same as Zytiga label, and most of the other the defendants' ANDA

labels?
A. Yes, essentially the same.
Q. Does section 5.1 contain any directions to administer prednisone to mitigate any side effects of abiraterone acetate?
A. No.
Q. Is section 5.1 of Mylan, Teva and Amerigen's ANDA labels different compared to the other labels?
A. No.
Q. Let's look at the Mylan label, for example, did you prepare a demonstrative exhibit demonstrating --
A. Yes.
Q. -- showing section 5.1 --
A. Yes.
Q. -- showing "warnings and precautions"?
A. Yes.
Q. Please turn to PDX --
THE COURT: Definitely.
Q. 4.61.
The last sentence here states, "co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) thrive, resulting in reduction in the incidents and severity of these adverse reactions." Is that sentence present in the 2018 Zytiga label?
A. No, it's not. That's a mistake that I made. I wasn't sure which labels actually failed to remove that.

Q. Understood. There are a lot of labels.

Does this language direct the use of 10 milligrams per day of prednisone to address mineralocorticoid excess related to abiraterone acetate?

A. No.

Q. As a physician, what do you make of the removal of this sentence from the Zytiga label?

A. As a physician, what it is telling me is that the FDA did not feel that it was necessary to include in the updated label.

Q. What impact does the inclusion of the co-administration sentence in Amerigen, Mylan and Teva's labels have on the infringement analysis?

A. No impact.

Q. Can prednisone mitigate abiraterone acetate's side effects, in addition to providing anti-cancer benefits?

A. Absolutely. It's really wonderful in that regard. It has an anti-cancer effect but, also, this added benefit.

Q. Are you aware that Ms. O'Shea testified that FDA recently ordered Teva to remove this co-administration of a corticosteroid language from its label, and the FDA will likely order Mylan and Amerigen to do the same?

A. Yes.

Q. I would like to return to one point, we talked about section 5.2 of the "warnings and precautions" section before. And I think you referred to the fact that, in your view,

exogenous corticosteroids make the adrenal gland fall asleep?
A. Yes.
Q. What makes the adrenal gland wake up or what is the next step, so to speak, after prednisone withdrawal?
A. So when prednisone is withdrawn and there are -- there are going to be lower circulating glucocorticoids, and that is recognized in the brain. And what happens is, specifically, the base of the brain, the hypothalamus and the anterior pituitary, the pituitary receives that signal and starts to make the hormone that we heard about a few days ago called ACTH, and that's the hormone that governs all the steroid production in the adrenal gland. When that gets to the adrenal gland, the adrenal gland says, okay, I'm going to start to make more steroids, and that's the way this thermostat is sort of reset when steroids are withdrawn.
Q. And just to be clear, abiraterone acetate is not causing the adrenal gland to fall asleep or any adrenal function?
A. No, it's the prednisone.
MR. KRAUSE: If we could put PDX-4.61 back up.
Q. Again, this is relating to section 5.1 of the "warnings and precautions" section.
What condition does section 5.1 generally relate to?
A. The condition of mineralocorticoid excess.
Q. What drugs can be used to manage mineralocorticoid excess?
A. So typically what one would do is manage the specific

complication. As an example, hypokalemia, which means low serum potassium, could be managed very simply with dietary supplementation. So what I do is, I watch the potassium very carefully, if it starts to go down I say, hey Mr. Smith, why don't you eat another banana or two per day and that usually takes care of it. Hypertension is managed with well tolerated antihypertension, either increasing a dose that they're on or adding a new one, pretty simple to do. And if they, on rare occasions, very rare, I've had to introduce that drug we talked about before, Eplerenone, the mineralocorticoid receptor antagonist, which blocks, effectively, the action of the mineralocorticoid as they exist in excess.

Q. How does the toxicity of Eplerenone compare to prednisone?

A. It's well tolerated and it would be my choice to use, as opposed to adding glucocorticoids or increasing dosage of glucocorticoids. That's what I have always done whenever I have -- I have never increased the dosage of prednisone beyond 10 milligrams to treat mineralocorticoid excess. And in the Phase I studies a protocol allowed for management of mineralocorticoids -- mineralocorticoid excess, excuse me, with Eplerenone first. That was the first choice in the overwhelming majority of patients who needed management of the mineralocorticoid excess received Eplerenone.

Q. And why would you choose the use of Eplerenone over prednisone?

A. It's just more well tolerated. There are literally thousands of papers that cite that long -- acute, sub-acute and chronic toxicities associated with prednisone and other glucocorticoids.
Q. What does the fact that the labels direct the use of prednisone, rather than Eplerenone, indicate to you about prednisone's role with abiraterone acetate?
A. In the warnings and precautions it doesn't tell me anything about the role of prednisone in abiraterone acetate.
Q. What do you make of the fact that defendants' ANDA label identify abiraterone acetate's mechanism of action, but do not identify that of prednisone?
A. My understanding is that there's the -- a requirement that the only mechanism action that's described is that of the labelled drug, which is Zytiga. That's my understanding.
Q. Why do you think it only shows the mechanism of action of the label drug?
A. That's what they're trying to get approved. That's the -- prednisone has already been out there on the market. It's a generic drug produced by many different manufacturers. So it's really all about, largely, a Zytiga label. It doesn't mean prednisone isn't part of the anti-cancer effect.
Q. How does the content of the mechanism of action section impact the meaning of the indications and usage section?
A. They're unrelated. In my view, they're separate and

independent.
Q. Defendants argued in their pretrial brief that they do not have specific intent to induce infringement because prednisone has never been FDA approved as an anti-cancer agent. Among practicing physicians is there a term for uses of the therapy that are considered not FDA approved?
A. Off-label.
Q. And what are some examples of off-label use, from a physician's perspective?
A. Using different dosages, using different formulations, let's say, an IV as opposed to an oral formulation. Different patients, different diseases.
Q. So, for example, giving a drug indicated for prostate cancer to a patient who doesn't have prostate cancer?
A. Right, breast cancer. Yeah.
Q. What materials do physicians look at to determine whether they are using a therapy on-label?
A. They use the indications and uses section.
Q. Have you analyzed, from a physician's perspective, whether the asserted claims cover an off-label use of Zytiga and defendant's generic abiraterone acetate?
A. Yes.
Q. What did you conclude?
A. That -- I'm sorry can you please repeat the question?
Q. Sure. Have you analyzed, from a physician's perspective,

whether the asserted claims cover an off-label use of Zytiga and defendants' generic abiraterone acetate?
A. Yes, they don't cover an off-label use.
Q. And why do you say that?
A. Because they cover that which is FDA approved, which is what is in the indications and usage section, which is, the combination of abiraterone acetate and prednisone for treatment of mCRPC.
Q. What would a physician, reading the Zytiga label and the defendants' labels, understand should be used for the safe and effective treatment of mCRPC?
A. The combination of abiraterone and prednisone.
Q. Do the defendants' labels or Zytiga labels suggest that abiraterone acetate, alone, is safe or effective to treat mCRPC?
A. No.
Q. Do the defendants' labels or the Zytiga labels suggest that prednisone, alone, is safe or effective to treat mCRPC?
A. No.
Q. From the perspective of a physician, is using prednisone as an anti-cancer agent with the defendants' generic abiraterone acetate, an off-label use?
A. No.
Q. Are you familiar with the labels for prednisone products?
A. Somewhat, yes.

Q. Is prednisone indicated for mitigating fluid retention, hypokalemia or hypertension?
A. No.
Q. In your perspective as a physician, is prednisone approved as a stand alone monotherapy to treat any type of prostate cancer?
A. No.
Q. Does the fact that prednisone is not approved to treat prostate cancer as a stand alone therapy suggest to you that prednisone is not approved to treat prostate cancer with abiraterone acetate?
A. No.
Q. In your experience, can two drugs have effects in combination that they would not have separately?
A. Yes.
Q. Are drugs sometimes approved in combination to treat cancer when neither drug is approved as a stand alone therapy?
A. Very frequently.
Q. What are some examples of that?
A. Combination chemotherapy is an example. There are many examples in the literature where monotherapy doesn't work. But the two in combination, for example, Gemcitabine and Platinol for lung cancer, or with Gemcitabine and other agents for ovarian cancer, in combination with Taxol for breast cancer. Those are example where both drugs are used in combination,

where one of them may not have much activity.
Q. In their pretrial brief, defendants argue that the use of prednisone with abiraterone to mitigate abiraterone side effect is a substantial non-infringing use. Can prednisone mitigate abiraterone acetate side effect, in addition to providing cancer effects?
A. Sure, I think it's just a -- just an added benefit. You have an anti-cancer effect and, by the way, you also have this effect on managing potential adverse effects of another drug.
Q. How, if at all, did the mitigation of side effects impact your conclusion that defendants' induce and contributorily infringe the '438 patent?
A. It does not.
Q. Do physicians expect any therapy to be effective in 100 percent of patients?
A. No.
Q. In your experience, are FDA approved therapies effective in every patient?
A. No.
Q. Let's turn to prednisone's anti-cancer effect. Does prednisone have an anti-cancer effect when administered at a dosage of 10 milligrams per day of prednisone in combination with 1000 milligrams per day of abiraterone acetate?
A. Yes.
Q. Have you prepared a demonstrative listing the principle

evidence that you've seen that prednisone has an anti-cancer effect, when administered in combination with abiraterone acetate?

A. Yes.

Q. If we could put up PDX 4.62.

Doctor, what is the principle evidence that prednisone has an anti-cancer effect when administered with abiraterone acetate?

A. So I think what you see here -- first off, I'll state this, that this whole pathway from hypothesis to hypothesis testing confirmation, is really the epitome of clinical and translational science.

This is how it should be done. You make a novel hypothesis, as Dr. de Bono did, for the mechanism for the anti-cancer effect of the combination, and then you start to test it. You learn about safety and you -- and in the confirmation studies it was the extension study. And therein, Dr. de Bono established that the hypothesis was accurate, literally in patients. That's not easy to do.

And then he went on to -- later phase studies, additional phase I and phase II studies, that showed that the combination of abiraterone with prednisone has a more durable effect on patients with metastatic castration-resistant prostate cancer than abiraterone acetate alone. A more durable effect that would be far greater than that which would be

expected by the simple addition of prednisone.

And then finally, sort of the epitome of the culmination of this process, was the phase III clinical trials that are required for regulatory approval and that's the 301 and 302 and eventually the LATITUDE studies.

Q. Let's talk about how prednisone provides an anti-cancer effect in combination with abiraterone acetate. And I'd like to focus on what is known today as opposed to what was known back in 2006?

A. Okay.

Q. You explained earlier that the androgen receptor of the prostate cancer cells is typically activated by androgens. Remember that?

A. Yes.

Q. What are mutated androgen receptors?

A. What's referred to -- in that term, mutated, are androgen receptors have a mutation in a particular region or domain of the androgen receptor and that's the domain that interacts with androgens. And what happens is when that domain is mutated, it can start to be activated by non-androgen chemicals, other steroids, as an example, and that's called promiscuous activation of the androgen receptor.

THE COURT: May I ask you, does the mutation occur in response to abiraterone?

THE WITNESS: So there are two ways it can occur. It

has -- it's called -- two theories either clonal expansion or clonal evolution. Expansion means that it pre-existed and under the selection pressure of the therapy --

THE COURT: That its competition is being wiped out?

THE WITNESS: Exactly. And the other one is that a mutation arises and then that's the one that goes out. But it is -- you are correct, Your Honor, that it's really a response one way or another to the abiraterone acetate. To the pressure, the selection pressure.

THE COURT: All right. Go ahead.

BY MR. KRAUSE:

Q. Are some steroids produced in the body upstream of androgens in the steroid biosynthetic pathway?

A. Yes.

Q. What impact do the upstream steroids have on prostate cancer growth when the androgen receptor is mutated?

A. Well, these are the kinds of hormones that can promiscuously activate it that the mutated andro receptors. In so doing, they can drive the growth of the cancer. The proliferation survival of the cancer.

THE COURT: You may be taller than the average lawyer? Is that on? (Discussion off the record.)

Q. What impact do the upstream steroids have on a prostate cancer growth when the androgen receptor is mutated?

A. As I said, these are the steroids, these upstream

steroids, that can activate the mutated adrenoceptor in a promiscuous fashion and in so doing, drive proliferation survival with the net effect of increased growth. So it causes the cancer to get worse.

Q. What effect does prednisone have on the production of upstream steroids when given in combination with abiraterone acetate? (Discussion off the record.)

A. It reduces the concentrations, the production and concentrations of those upstream steroids.

Q. Is 10-milligram per day of prednisone, when given in combination with 1000 milligrams per day of abiraterone acetate, sufficient to achieve this reduction in upstream steroids you're discussing?

A. Yes.

Q. Is 10 milligram per day of prednisone, when given in combination, given with 1000 milligrams per day of abiraterone, sufficient to achieve an anti-cancer affect?

A. Yes.

Q. Is the mechanism of prednisone with abiraterone acetate, that you've described, been reported in the literature?

A. Yes.

Q. If you could please turn to PTX-344.

A. Got it.

Q. Do you recognize this document?

A. Yes.

Q. What is it?
A. This is an article, a manuscript, in a journal called The Oncologist, a peer reviewed, well-read journal, describing new treatment strategies for metastatic prostate cancer in patients who've already had chemotherapy with docetaxel.
Q. Did you rely on this document in forming your opinions?
A. Yes.
Q. And what year was it published?
A. This was published in 2011.
Q. And what journal was it published in?
A. The Oncologist, a peer reviewed journal, well respected, well-read journal.
Q. Please turn to Page 1495 and look at the first paragraph under the heading biomarkers of abiraterone anti-tumor activity.
A. Got it.
Q. What clinical studies of abiraterone acetate is this passage referring to?
A. So this is reference 55, which is the Attard 2009 paper. Which is -- yes -- yes, 55 is reference -- that was published in 2009 in cancer research.
Q. Is that referring to the extension study of Dr. de Bono?
A. You know I think this -- no, that particular study is not. That's not the actual study. I think there's a typo within the reference because that is not -- not the Attard 2009 clinical

trial.
Q. Okay. And if we could -- I'd like to refer to the portion -- a portion -- read a portion of the paper. It states, in part, low dose steroids were successfully used to decrease production of ACTH and upstream steroids at disease production on abiraterone acetate alone. Low dose steroids inhibit the ACTH feedback loop and upstream steroid precursor synthesis which can active promiscuous AR.

What is that passage referring to?

A. This is referring to Dr. de Bono's hypothesis. This is the restatement or recapitulation of that hypothesis.

Q. And how does the reference to ACTH relate to this mechanism?

A. As I said, ACTH is what's driving the increased concentrations of the upstream steroids and prednisone is what's pushing it back down.

Q. If you could please turn in your book to JTX-8084?

THE COURT: Before you do it, let me ask one more question. I think I know what upstream steroids means, but why don't you define it for me?

THE WITNESS: Sure. So if you think about adrenal steroids you can think about them in a simplistic way in a hierarchy. The starting point to make all steroids is actually cholesterol. And at the first step when cholesterol is converted to its product, that is a precursor for largely

mineralocorticoid. The next step when the product of cholesterol is turned into its own product, is the precursor for the synthesis of glucocorticoids, like cortisol. And finally, the final step is the conversion into the weak adrenal androgens. Now it's important to understand that these categorizations of mineralocorticoids and glucocorticoids are somewhat artificial.

Because many of these -- so when I say upstream really what I'm talking about is upstream of the enzymatic block, the dominant enzymatic block of abiraterone acetate. So these include those hormones that are more proximal to the cholesterol, the first steps, if you will. And those hormones can build up as a consequence of the enzymatic block, we'll call them upstream steroids or upstream hormones, and those are the ones that can activate the mutated androgen receptors, as Dr. de Bono described it.

And the prednisone, by giving it to the patient, it's shutting off the signal that's induced by the abiraterone acetate to make the extra upstream steroids. Does that make sense?

THE COURT: Yeah. You mean upstream, for example, of CYP-17, right?

THE WITNESS: Exactly.

THE COURT: Go ahead.

BY MR. KRAUSE:

Q. Please turn in your book to JTX-8084.

Do you recognize this document?

A. I sure do.

Q. What is it?

A. This is a commentary by de Bono and colleagues in *Cancer Cell*.

Q. And what year was it published?

A. 2009.

Q. And where was it published?

A. *Cancer Cell*. This is one of the premier journals in cancer research. It only publishes the highest impact studies and is a very rigorous peer-review process.

Q. What do you mean by high impact?

A. Well-read and well-cited.

Q. Please turn to Page 460 and look at the middle paragraph of the second column.

A. Okay.

Q. There the paragraph says in part: Although alternatives are possible, these data suggest that AR signalling was initially abrogated by suppression of androgen LBD and estrogens downstream of CYP17 and, subsequently, reactivated by a rise in the level of upstream steroids driven by high levels of adrenocorticotropic hormones that are suppressed by endogenous corticosteroids.

What is that referring to?

A. Again, this is just a restatement of the hypothesis -- just another way of restating the de Bono hypothesis. I just point out LBD stands for ligand binding domain, LBD, and that's the domain that becomes mutated and can respond to nonandrogen hormones, or ligands.

Q. What does the concluding sentence, quote, overall, these observations support the current clinical development of abiraterone acetate in combination with prednisone, closed quote, mean?

A. So it's saying, okay, we've established the mechanism as a real phenomenon, and now we're going to further try to get -- develop the combination of abiraterone acetate and a glucocorticoid, in this case, prednisone, in more advanced phase clinical trials.

Q. If you could, please turn in your book to JTX-8090 now.

A. Got it.

Q. Do you recognize this document?

A. I do.

Q. What is it?

A. This is what's referred to as the Danila paper. It's a Phase II multicenter study of abiraterone acetate plus prednisone in patients who had received docetaxel and were castration resistant.

Q. And what year was this published?

A. 2010 through the *Journal of Clinical Oncology*.

Q. And what's your opinion of the *Journal of Clinical Oncology*?
A. It's essentially one of the top few premier oncology journals to disseminate important clinical observations. I think out of 173 oncology journals, it ranks fourth.
Q. What does JTX-8090 describe?
A. It's describing this Phase II study of abiraterone plus prednisone, with the prednisone being used from the get-go, and in patients with metastatic CRPC who had had docetaxel chemotherapy and describing the responses to that combination treatment.
Q. What dosages were administered in the trials described in JTX-8090?
A. 1000 milligrams of abiraterone acetate and 10 milligrams of prednisone.
Q. Is that the same amount as appears in defendants' labels?
A. That's correct, yes.
Q. Please turn to Page 1497. Do you see the sentence here, the bottom of the first column beginning, Importantly?
A. Yes.
Q. The sentence provides: Importantly, the evaluation of this steroid combination was further supported by our work indicating that low-dose steroids can reverse clinical AA resistance and decrease steroid precursors upstream of CYP17 that can activate AR signalling.

What is that referring to?

A. So this is basically saying that we have previous clinical empiric evidence that the hypothesis is true. It's referring to the extension -- 001 extension study where steroids were added to abiraterone acetate at the time the abiraterone acetate stopped working.

Q. And we say the hypothesis. Is that referring to Dr. de Bono's hypothesis?

A. Yes, of course, Dr. de Bono's hypothesis.

Q. What do the articles that we've discussed tell you about Dr. de Bono's hypothesis?

A. That it was being disseminated widely to the research community, and that it was true.

Q. What does the fact that the de Bono hypothesis was published in these particular scientific journals say about the hypothesis' acceptance by the scientific community?

A. That it was very important, because the reviewers and the editors of these journals have to make a decision about which manuscripts to select, and these are the most prestigious, so only a small percentage get in.

So it's telling us that the publication in these journals is very important, and let's get it out to the broad oncology community as much as possible from these wide -- in these wide-spread -- wide-read journals.

Q. Let's turn next to the clinical studies of abiraterone

acetate. If you'd please look in your binder at JTX-8083 and tell me what that document is?

A. Okay. This is the Attard 2008 paper. That's how we refer to it. It's the Phase I clinical trial of abiraterone acetate in CRPC patients.

Q. And this is also in the Journal of Clinical Oncology. Is that right?

A. That's correct.

Q. If you could also turn to JTX-8086 in your binder and tell me what that is.

A. This is Attard 2009, so it's a follow-up where they had a little bit more Phase I and then Phase II data and an additional extension phase data. This is -- that's what this study is also published in *Journal of Clinical Oncology*, but this was published in 2009.

Q. And did you rely on JTX-8083 and JTX-8086 in forming your opinions?

A. Yes.

Q. And I believe you referred to JTX-8083 as Attard 2008, and JTX-8086 as Attard 2009. Is that correct?

A. Yes, I did.

Q. What does Attard 2008 describe?

A. It's describing a Phase I dose escalation study in which patients were receiving abiraterone acetate at increasing doses, and the purpose was largely to establish safety and

effects on hormone levels of the various doses that were tested to identify, ultimately, a dose that should be used or selected for Phase II, or recommended Phase II dose.

It also describes clinical responses to --

Q. What does Attard 2009 describe?

A. That is describing more of the Phase I data, but also is really focused on the Phase II, and so it's describing the use of a specific dose of abiraterone acetate, the dose that was selected for further development at 1000 milligrams a day, and the prednisone was already set at 5 milligrams twice a day.

Q. If we could look at JTX-8083 first, and if I could ask you to turn to Page 4565 and look specifically at the second column, first paragraph, first sentence, Page 4565.

A. I'm sorry, which column and paragraph?

Q. Second column, first paragraph, first sentence.

A. Got it.

Q. Attard 2008 states there: This study was also prospectively designed to allow the addition of dexamethasone (0.5 mg daily) to abiraterone acetate in all patients at disease progression to test the hypothesis that resistance could be reversed by suppressing ACTH by decreasing upstream androgenic steroids that could activate a mutated promiscuous AR, closed quote.

What is that referring to?

A. It's referring to the notion that the study was designed

to confirm the de Bono hypothesis. So we're really talking about the extension phase of the study where patients had progressed on abiraterone acetate by itself and then a corticoid steroid, in this case, dexamethasone. It's really -- they're all interchangeable in terms of their effects on upstream steroids, so that's what this is describing.

Q. How did the extension study design allow researchers to know if a glucocorticoid actually reversed resistance to abiraterone acetate?

A. So I think the -- one of the lines of evidence, I think is the strongest, was the extension study where there was a subgroup of patients who had actually had the same dosing schedule of dexamethasone prior to the abiraterone acetate and had progression on the dexamethasone. The cancer got worse. They got the abiraterone acetate, and eventually cancer gets worse.

So they have two drugs, neither of which was working, and then patients are kept on the abiraterone acetate on the same dosing schedule dexamethasone was then used, and added back in the extension part, and responses were elicited. So this was a -- that's -- that's how it worked.

Q. I think we heard earlier that PSA was used in these studies?

A. PSA was one measure that was used, yes.

Q. And how is PSA used in prostate cancer research?

A. I'm sorry?
Q. How is PSA used in prostate cancer research?
A. So it is used as a marker of potential clinical benefit. It's especially useful in developing drugs that have a hormonal-based mechanism of action such as abiraterone acetate and prednisone.

And the reason why is because the PSA gene itself is regulated by the androgen receptor. So when we see the PSA going down, that is a signal that the androgen receptor is being inhibited. It's basically -- the therapy is hitting its target, if you will. So it's a very good signal, no-go -- I'm sorry -- go-no-go signal in drug development for androgen therapies.

Q. Okay. Please turn to Figure A1 in Attard 2008, which is JTX-8083.
A. Figure --
Q. It's at the very end.
A. Yes. Got it.
Q. Have you analyzed these figures?
A. I did.
Q. And what do these figures generally depict?
A. These are depicting PSA levels on the vertical axis versus time on study on the horizontal axis.
Q. Were you in the courtroom when Dr. de Bono provided his interpretation of these figures?

A. Yes.
Q. Do you agree with Dr. de Bono's description of Figure A1 of Attard 2008?
A. Yes.
Q. How would you characterize the response these patients had after a glucocorticoid was added to abiraterone acetate?
A. Very unexpected. Stunning, if you will, and confirmatory, in my view, of the hypothesis.
Q. Why is that?
A. Again, it's the -- going back to Dr. de Bono's, the A plus B, if A is not working, B is not working, A plus B works. So it's telling us that the hypothesis is now being manifested in patients. We're seeing a real live example of this, and it's seen in these two patients, as well as other patients in the extension study.
Q. How common, in your experience, is it to see a combination of two therapies that don't work individually work together?
A. Rare times rare times rare. I have -- at that point, this was unprecedented. I had never seen this before, so this was a really, really clever design, actually, to use such a -- to require a relatively few number of patients to confirm a very novel and interesting hypothesis, in my view.
Q. Doctor, in your view, what other explanation could there be for the results in Figure A1 of Attard 2008 other than both the glucocorticoid and abiraterone acetate provide an

anti-cancer effect?
A. None, really. I mean, this is the conclusion that I would make is that de Bono's hypothesis is correct.
Q. If you could please turn to Page 4568 of that same paper and look at the section entitled, "Reversal of Resistance."
A. Okay.
Q. How many patients in Attard 2008 responded after a glucocorticoid was added to abiraterone acetate?
A. The addition of dexamethasone resulted in successful salvage in four of 15 patients who had progressed by PSA working group criteria on abiraterone acetate alone. That lasted those number of days, as indicated there. All four patients have an ongoing response, and two of the four had previously, also, received single agent dexamethasone.
Q. Now please turn your attention to Attard 2009, which is JTX-8086, and turn to Page 3745, the section entitled "Addition on Corticosteroids At Progression On Abiraterone Acetate Alone."
A. Okay.
Q. How many patients in the Attard 2009 extension study had progressed on dexamethasone alone and abiraterone acetate alone before being provided with dexamethasone again in combination with abiraterone acetate?
A. So it looks like if the patient -- the number of patients who had had both prior to getting the dexamethasone back was 11

total, and four responded, 36 percent.

THE COURT: I'm sorry, I didn't get that. Say that again.

THE WITNESS: Could you repeat the question so I answer?

BY MR. KRAUSE:

Q. Sure. How many patients in the Attard 2009 extension study had progressed on dexamethasone alone and abiraterone acetate alone before being provided dexamethasone again in combination with abiraterone acetate?

A. A total of 11 patients and four responded, 36 percent responded.

Q. And that 36 percent had a PSA decline of greater than 50 percent?

A. That was the criteria for response, yes.

Q. How common is that criteria for response?

A. That's a pretty standard criteria. It's in the PSA working group criteria, prostate cancer working group criteria, yeah. That's the standard.

Q. Please turn to Attard 2009, Page 3747. Let's look at the first full paragraph. The first sentence states, "We have not previously observed, and to our knowledge, there are no published reports of secondary responses to reinstitution of single-agent dexamethasone in patients who had previously experienced progression on this therapy."

What does that sentence in this paragraph in general tell the reader?
A. So they're stating what I indicated earlier, which is this is unprecedented where you had dexamethasone not working, another drug not working, and then let's add that to the dexamethasone. So this was an entirely new approach to establishing a hypothesis, in this case, the de Bono hypothesis, and the patients have served as essentially their own internal control. Really, really neat.
Q. What glucocorticoid was used in the extension study?
A. Dexamethasone.
Q. What, if anything, does a study combining dexamethasone with abiraterone acetate tell a physician about what would happen if prednisone were combined with abiraterone acetate?
A. That it would achieve the same effect, because as long as we use a sufficient dosage, prednisone and dexamethasone will both suppress the ACTH-driven excess of upstream steroids. So these -- whether it's dexamethasone or prednisone, it's a class effect. It's a class effect on the upstream steroids so they're interchangeable for the purposes of this effect.
Q. Let's move on to other evidence regarding the efficacy of the combination. If you could turn in your book to JTX-8093.
A. Got it.
Q. Do you recognize this document?
A. Yes.

Q. And what is it?
A. This is the -- what we call the "Ryan 2011 Paper". It's the phase II study of abiraterone acetate plus prednisone in patients who are castration-resistant who have not yet had chemotherapy, are called chemotherapy naive.
Q. Did you rely on JTX-8093 in forming your opinions?
A. Yes.
Q. When was it published?
A. 2011.
Q. And where was it published?
A. Clinical Cancer Research.
Q. What is Clinical Cancer Research?
A. It's, also, a high-impact journal -- it's a journal of one of the -- that's published by the American Association For Cancer Research and it publishes important and high-impactful articles.
Q. And what does this reference, "Ryan 2011," describe?
A. It is the phase II study of abiraterone acetate with Prednisone at the start for patients with mCRPC who have not yet had chemotherapy.
Q. How does the design of the Ryan 2011 Study differ from the extension study described in Attard 2009?
A. The prednisone is the -- in this case, the glucocorticoid, which is prednisone, was given at the start when this clinical -- when the Clinical Trial therapy was started. So

abiraterone acetate and prednisone were given from the get-go, as opposed to the corticosteroid prednisone here, given at the time that the abiraterone acetate stopped working.

Q. And what doses of abiraterone acetate and prednisone were administered in the Ryan 2011 study?

A. That would have been a 1000 milligrams of abiraterone acetate and 10 milligrams total per day of prednisone.

Q. And was time to PSA progression an endpoint in the Ryan 2011 study?

A. Yes.

Q. What is time to PSA progression?

A. It's the time that it takes for the PSA to start increasing from some level. So the PSA can go down and reach its lowest point or nadir, and it's the time, for example, from that nadir to when the PSA goes up. And it's -- how much it goes up is defined by these PSA working group criteria.

Q. What does "time to PSA progression" tell physicians about whether a patient is responding to therapy?

A. It is an important measure of it, because as it's implied in it's name, "time to PSA progression." It's a measure of the durability effect. So, for example, you can have a very deep decline in PSA, the PSA goes down by 99 percent, and if that lasted two weeks and the next time in 2 weeks the PSA is 10 times what it was at baseline, that's not very impactful on the patient. But if the PSA goes down and stays down without going

up for a durable period of time, that can translate well into an overall survival benefit.

Q. Is there a relationship between time to PSA progression and overall survival for prostate cancer?

A. Yes, there is.

Q. If you turn to your binder to PTX-154.

A. Got it. Sorry -- I have it.

Q. Do you recognize PTX-154?

A. Yes.

Q. What is it?

A. This is an analysis of the controlled abiraterone acetate study, the randomized controlled trials of abiraterone acetate to try to correlate PSA change -- PSA measurements, measurements of PSA with overall survival.

Q. Did you rely on this document in forming your opinion?

A. Yes.

Q. Could we refer to PTX-154 as XU-2015?

A. Yes, and this was published in, also, in *Clinical Cancer Research*, the *AJCR Journal*, *American Journal of Cancer Research*, a very prestigious journal.

Q. What clinical trial data was the analysis, XU-2015 based on?

THE COURT: XU, by the way, "X-U", correct?

THE WITNESS: X-U.

MR. KRAUSE: I apologize.

THE WITNESS: So these data were based on the 301 and 302 studies. Those were the randomized controlled trials of abiraterone acetate and prednisone that led to initial regulatory approval, both in the post-chemo and pre-chemo therapy settings, respectively.

Q. Let's look at the abstract under "results." It states there, "The effect of AA on PSA kinetics were significant (P less than 0.0001) and comparable between the chemotherapy-naive and -pretreated patients. PSA kinetics [e.g., PSA nadir, PSA response rate (greater than or equal to 30 percent, 50 percent, and 90 percent), time to PSA progression, PSA doubling time (PSADT)] were highly associated with OS in both populations."

What is this telling the reader?

A. So what this is telling the reader is that "AA" -- and this is a shorthand for abiraterone acetate plus prednisone, it's just the nomenclature that's used here -- "changes in PSA" including those that are listed there which, also, includes time to PSA progression, are highly associated with overall survival in both populations, and that significance is statistically described in that "P value," P less than 0.0001. So that's kind of like saying there's a less than 1 in 10,000 chance that those results occurred by chance.

Q. Did you prepare a demonstrative comparing the "time to PSA progression" values reported in Attard 2009 with those in Ryan 2011?

A. Yes.
Q. If we could turn to PDX 4.63.
MR. KRAUSE: Display that, please.
BY MR. KRAUSE:
Q. What does the first row of PDX 4.63 show?
A. So this is the 001 Study data that are looking at the time to PSA progression for the patients when they were on abiraterone acetate by itself. So these data are not incorporating the extension phase where the dexamethasone was added at the time of the disease progression. Just looking at the time to PSA progression on abiraterone acetate by itself. And what it shows, is that the median "time to PSA progression" was 7.5 months or 225 days.
Q. That's referred to as the Clinical Trial or the 001 Trial; is that correct?
A. Yes, that's the Attard 2009. It's either 001, Attard 2009.
Q. And, again, that's abiraterone acetate monotherapy and that was published in Attard 2009?
A. Correct.
Q. Okay. And what does the second row of PDX 4.63 show?
A. So these are the data from the Ryan 2011 Study, what we are calling the 002 Study, same type of patients in that their mCRPC haven't had chemotherapy yet, but here they're reporting the time to PSA progression for patients who had abiraterone

acetate and prednisone from the start. From what you can see, is that there's a marked improvement in the "time to PSA progression," so abiraterone acetate by itself was seven and a half months and prednisone from the start more than doubled that from -- to 16.3 months or 497 days.

Q. What do you conclude from comparing time to PSA progression in Attard 2009 with Ryan 2011?

A. That using prednisone with abiraterone acetate from the start has a meaningful and clinical -- a clinically meaningful impact on time to PSA progression. So it is adding a clinical benefit that was not observed with abiraterone acetate by itself.

Q. Did you prepare a demonstrative comparing Figure 3 in Attard 2009 with Figure 2 in Ryan 2011?

A. I did.

Q. If we could pull up PDX 4.64. What is shown in these figures?

A. This is, basically, showing the "time to PSA" analysis over time in the two studies. On the left is Attard 2009 and on the right is the Ryan 2011 Studies.

Just to refresh everyone's memory, in the Attard 2009 data this is the abiraterone acetate only component of that and in the Ryan 2011, this is abiraterone acetate plus prednisone.

Q. How do these data compare?

A. Well, you can just look at the curves. The curve on the

left is much steeper. In other words, patients are manifesting from PSA progression more rapidly than the curve on the right, which is less steep.

Q. What does this mean?

A. It's telling us, this is a graphical manifestation of the median time to progression data. And it's telling us that the combination of abiraterone acetate plus prednisone is resulting in a longer time to progression.

Q. Do you see in figure 2 of Ryan 2011 the statement "median days 497"?

A. Yes.

Q. And what does that refer to?

A. A median, so that means half the patients had disease progression after 499 -- 497 days and the other half had their PSA get worse before 497 days. That's what the median means.

Q. For comparison, how many patients on abiraterone acetate monotherapy, in Attard 2009, had progressed at 497 days?

A. It looks like one. So if you look at the vertical axis, and you see 480, to the right of that would be 497, and at the very end of that there is one little tick representing that last patient.

Q. So every patient in that study, except for one, had progressed?

A. Yes, that's correct. By the median time to progression in Ryan 2011, when the combination was given from the start, only

one of all the patients in Attard 2009 had not yet manifested PSA progression.

Q. What do you conclude from comparing Figure 3 in Attard 2009 with Figure 2 in Ryan 2011?

A. The combination is really helpful to achieve the maximum clinical benefit.

Q. Do the Attard 2009 and Ryan 2011 Papers describe separate clinical studies?

A. They do.

Q. Is it appropriate to compare the results of different clinical studies?

A. Sure, it can be.

Q. Is a comparison of the time to progression results from Attard 2009 and Ryan 2011 valid?

A. In my view, yes.

Q. Did you consider whether any differences between the Attard 2009 and Ryan 2011 Studies might account for the difference in results?

A. Sure, yes.

Q. And what did you conclude?

A. That they can't account for this magnitude of difference.

Q. How do the patient populations in the Attard 2009 and Ryan 2011 Studies compare?

A. In my view, overall they were similar. These were patients with metastatic CRPC who, for the most part, who had

not yet had chemotherapy.
Q. Could difference in the patient populations between the two studies explain the differing outcomes of the studies?
A. Not in my view, when I look at the baseline characteristics of these two -- baseline characteristics of the patients in these two studies.
Q. Did you prepare a demonstrative comparing the patient populations?
A. Yes.
Q. Let's look at PDX 4.65. What does PDX 4.65 show?
A. Some of the most important baseline characteristics that may predict for clinical responses to a therapy in prostate cancer. So that's what this is showing, and it's comparing the characteristics of those four factors in the Attard 2009 to the Ryan 2011 Papers.
Q. How did patients' previous history of chemotherapy compare in the Attard 2009 and the Ryan 2011 Studies?
A. Neither had chemotherapy, they're the same.
Q. Why did you consider whether patients had prior chemotherapy?
A. Prior chemotherapy will alter responses to subsequent therapy. So patients who have not had chemotherapy will have a better response to therapy, in general, as compared to patients who have already had chemotherapy. And that's a critical factor. And that's, in fact, why the FDA originally requested

a post-chemotherapy Phase III Study and a pre-chemotherapy Phase III Study.

Q. The next row in your table identifies "ECOG scores." What is an "ECOG Score"?

A. Eastern Cooperative Oncology Group Score, is a measure of performance, that's basically saying, how well is the patient doing. It's a scale of zero to five. "Zero" means they have the cancer, but have zero symptoms. "One" means they have minimal symptoms that are not affecting their activities of daily living. And at the other extreme, is "four" and "five." "Five" is the patient has died and "four" is the patient is bed bound.

Q. Please turn in your binder to PTX-31.

A. Got it.

Q. Do you recognize this document?

A. Yes.

Q. Did you rely on PTX-31 in forming your opinions?

A. Yes.

Q. And what does PTX-31 describe?

A. It's describing what happens to patients who have been treated with abiraterone acetate and prednisone who have -- based on their performance status, what we just talked about, their ECOG performance status.

Q. Look at the first page under the "results and limitations" the last sentence states, "on multivariate analysis, ECOG PS

was a significant factor for OS (P less than 0.001) time to PSA progression (P = 0.043) and PSA decline (P = 0.002)." What the does that mean?

A. So this is just another way of saying what I said, which is that the ECOG performance status is a predictor of responses, and in this case, outcomes as well. So the ECOG performance status is a factor that predicts for overall survival and, also, responses based on PSA, both the "time to PSA progression" as well as the PSA decline.

Q. If we could go back to PDX 4.65. How did the ECOG scores compare between Attard 2009 and Ryan 2011?

A. They're the same.

Q. Your demonstrative, also, refers to Gleason Score. What's a Gleason Score?

A. So Gleason Score is a pathologic grading system. It was, actually, invented by a pathologist at the Minnesota VA whose name was Gleason. And what it describes is this grading system specific for prostate cancer. And what grading is, is a way that the pathologist uses to determine how similar or dissimilar the cancer glands look as compared to normal glands.

Q. What is the significance of a Gleason Score for a prostate cancer patient?

A. So Gleason scores are another important predictor of responses to therapy and outcome, with higher Gleason scores being bad for the patient.

Q. Please turn in your binder to PTX-148. Do you recognize this document?
A. I do.
Q. And did you rely on PTX-148 in forming your opinions?
A. Yes.
Q. Please, turn your attention to the abstract, the second sentence tells us that, quote, Gleason Score, GS, is one of the best predictors of PCA aggressiveness.

What is that referring to?

A. It's a restatement of what I said, which is, the Gleason Score is really a good predictor of the biology of the cancer. When I say "biology," how fast it's going to grow; its impact on life expectancy, its impact on responses to therapy. So this is just a statement of that.
Q. If we could turn back to PDX 4.65.

THE COURT: Sorry, just tell me, Gleason scores run from what to what? One to --

THE WITNESS: Yes. So they're scored on a scale -- it would be from two to ten.

THE COURT: Two to ten, thanks.

BY MR. KRAUSE:
Q. How did the median Gleason Score compare between Attard 2009 and Ryan 2011?
A. They're the same. The median Gleason Score is the same.
Q. Let's look at the next row, "bone metastases" what are

"bone metastases"?
A. That means spread of the prostate cancer from the prostate to the bones. The bones are the most common site of metastases for prostate cancer and is -- the involvement of the bones in metastatic disease in that way is, also, an important predictor of response and survival.
Q. How did the frequency of bone metastasis compare between Attard 2009 and Ryan 2011?
A. No clinically significant difference.
Q. Why did you consider all these factors?
A. Because as I indicated, these are factors that are important to consider when comparing two populations. Because if these factors are markedly different, it can be difficult to do a cross study comparison. You're going to try to compare something from one study to another, say time to PSA progression you want to have a sense that there's no factor that would be so different amongst -- between the populations that would account for the differences in the result.
Q. Are you aware that defendants have alleged there are differences between the Attard 2009 and 2011 studies?
A. Yes.
Q. Did you consider those alleged differences?
A. I did.
Q. Did you prepare demonstrative summarizing some of the arguments raised by the defendants' experts?

A. Yes.
Q. If we could look at PDX 4.66. The first row, what does baseline PSA refer to?
A. The baseline PSA refers to what the PSA value is at the time the patients entered the study, started the study treatment. And what you see here is that the median PSA is actually higher in the 2009 compared to 2011. And when we look at PSA, it can be difficult to interpret. It's -- at first look one would say, okay, higher PSA, worst disease, but it turns out that more aggressive cancers produce less PSA per gram of tissues than less aggressive cancers. So these are in the general similar range. They're not log orders of magnitude different and I don't think that it's substantially different. And I couldn't tell you for sure which study its favoring but, if either one, but it may be just, in general, I don't think it's largely impacting the cross-trial comparison when we look at other factors.
Q. How do the baseline PSA level ranges compare between Attard 2009 and Ryan 2011?
A. Yeah, those ranges are very similar.
Q. What does that tell you about the patient populations?
A. That's another way of saying -- that's another factor that suggests that the populations are similar.
Q. How did the criteria for progressive disease compare between the two studies?

A. They used the same criteria called PSA working group criteria 1.
Q. And are those the working group criteria the criteria you referred to earlier in your testimony?
A. Yes, yes.
Q. How did the number of patients with lesions compare between the two studies?
A. They are similar. There's -- so what they're talking about lesions is really metastasis. So really all of the patients in Ryan 2011 had metastasis but a subset of patients, 10 percent, didn't. So this is a confusing concept. So the patients have castration-resistant prostate cancer but they don't have metastasis. The only manifestation of their disease is a rising PSA because their disease burden is too low to even be detected on a conventional scan.

So it's called non-metastatic castration-resistant prostate cancer. So if anything -- well we know that these patients do better, they don't have disease -- detectable disease. They have a much better outcome than patients with metastatic CRPC. So this particular parameter does favor the Attard study, the study that got abiraterone acetate alone.
Q. How does the four patient difference in the number of patients with lesions impact the comparisons of the results?
A. I don't think it's too much, but in anything it favors the 2009 patients.

Q. How did the number of patients compare between the two studies?
A. Similar. It doesn't affect my analysis.
Q. Had patients enrolled in both studies received prior hormonal treatment?
A. Yes. All of them. 100 percent of them were castrated and the overwhelming majority had also received anti-androgens. Those are the drugs that can sometimes be used second in line they're called androgen receptor antagonist they block -- they are just other hormonal therapies. Just another way of blocking male hormones.
Q. How did the number of patients previously treated with glucocorticoids compare across the two studies?
A. It was higher in the Attard 2009 than the Ryan 2011, but this also didn't impact my analysis and that's because of specific data from Attard 2009. And those data were the median -- the median time to PSA progression on abiraterone acetate only in patients who did have dexamethasone prior to going on abiraterone acetate and those that didn't. And those median "times to PSA progression" did not differ. So prior dexamethasone did not affect the median time to PSA progression in this particular study.
Q. How did the number of patients previously treated with Ketoconazole compare across the study?
A. Two patients versus zero. So again, a very small number

of patients in the Attard 2009, and that largely doesn't affect my analysis.

Q. Where did the Attard 2009 and Ryan 2011 studies take place?

A. Attard 2009 in the UK, and Ryan in 2011 in the U.S.

Q. Do you believe the difference in geographic location had an impact on the study results?

A. No. These are largely Caucasians with metastatic -- with castration-resistant prostate cancer.

Q. How did the number of study sites compare between the two studies?

A. There were more study sites in Ryan 2011 than Ryan 2009 but I don't think this affected the other parameter's that we discussed.

Q. Do Attard 2009 and Ryan 2011 report data on PSA declines?

A. Yes.

Q. Did you prepare a demonstrative summarizing those data?

A. Yes.

Q. If we could pull up PDX 4.57.

How do the PSA responses reported in Attard 2009 and Ryan 2011 compare?

A. So you can see here that the responses are higher in the Ryan 2011. So if you -- to simplify this, the PSA response in Ryan 2011 was about 80 percent and it was about two out of three in the Attard 2009.

Q. And so in Attard 2009, 67 percent of patients after 12 weeks of treatment. Is that right?
A. Yes, exactly. And then 79 percent means any time during the course of the therapy, including 12 weeks and after, there was a decline in PSA by 50 percent or more of 79 percent.
Q. In Ryan 2011, 67 percent before 12 weeks of treatment. Is that right?
A. Yes, that's correct.
Q. What is the significance of the PSA response rates in these studies as compared to time to PSA progression?
A. It's just another measurement of PSA that favors the combination of abiraterone acetate and prednisone.
Q. Are you aware that defendants have argued the difference in median time to PSA progression in Attard 2009 and Ryan 2011 may not be statistically significant because the confidence intervals overlap?
A. Yes.
Q. What is your understanding of confidence interval?
A. So a confidence interval is a range of values that gives you the likelihood that the value of interest will fall. So as an example, if you have a 95 percent confidence interval and you do a study 100 times to look at the median value, some median value, it will fall within that range 95 out of 100 times.
Q. Did you prepare a demonstrative to explain your opinions

on this issue?
A. Yes.
Q. If we could pull up PDX 4.68. What is shown here?
A. These are comparison of the time to PSA progression confidence intervals in the Attard 2009 and to the Ryan 2011 patients. And what it shows is the median, which we talked about, was 225 days with abiraterone acetate by itself and when prednisone is added it's more than doubled. And the confidence intervals overlap at the extreme. So the very highest part of the confidence interval of Attard 2009 overlaps, which is 287. Overlaps with the lower end of the 95 percent confidence interval of Ryan 2011 which is a little bit lower than that at 281 days.
Q. So about how many days overlap is there?
A. Six.
Q. Can data be clinically significant even though it's not statistically significant?
A. Absolutely. We can infer things from clinical trials as clinicians that may not reach arbitrary statistical value. It's important to note that the converse is true, that it is possible to have something that reaches statistical significance that doesn't have much clinical significance. If you do a big enough study with, let's say the whole population on the planet, you might get a statistically significant result, but it might not be that clinically significant.

Q. Even if you are unable to conclude that the medians are necessarily different due to the confidence intervals, would this change your opinions with respect to the experimental results?
A. No.
Q. What can you conclude from the comparison of the time to PSA progression reported in Attard 2009 and Ryan 2011 about the effects of administering prednisone 10 milligrams per day with abiraterone acetate 1000 milligrams per day?
A. That is playing a major contribution to the clinical benefit when adding the corticosteroid from the get-go more than doubles the median time to PSA progression when adding abiraterone acetate that seems to wellness is very impactful to me.
Q. Have you seen any difference between the Attard 2009 and Ryan 2011 studies that causes you to question whether a comparison of the time to PSA progression data is valid?
A. No.
Q. Are you aware that defendants have alleged that certain clinical data contradicts your opinions?
A. Yes.
Q. Did you consider that allegedly contradictory clinical evidence?
A. Yes.
Q. First, let's talk about defendants' argument that results

of COU-AA 001 and 001-EXT reported on the clinicalstrials.gov website were inconsistent with the data reported in Attard 2009. Why is the 11-month time to PSA progression reported on the clinicaltrials.gov website different from the 7.5 months reported for abiraterone acetate monotherapy for Attard 2009?

A. So at first blush it might seem contradictory but it's not. The reason why is because on the clinicaltrials.gov website, the data included the dexamethasone add back, the extension part. So that median time to PSA progression was abiraterone and then dexamethasone. Whereas, that which we just discussed at seven and a half months was just the abiraterone only. So, naturally, there will be a difference. It's not contradictory.

Q. Now let's talk about defendants' argument that the 004 study --

THE COURT: Pause for a moment. I sensed we were getting toward the end and we're at about 1 o'clock. If you're really going to a close let's push through, but if not, then perhaps we should take our break.

MR. KRAUSE: My guess would be, Your Honor, about another 20 minutes.

THE COURT: Let's take our lunch break then. I think everyone could use a break. Let's reconvene around 2 o'clock. Okay?

(Lunch recess taken at 1:04 p.m. to 2:00 p.m.)

THE COURT: All right. Be seated. Everybody ready? Let's proceed.

BY MR. KRAUSE:

Q. Dr. Rettig, there are a couple points I'd like to go back on quickly.

If we could pull up JTX-8086, Page 3745, and look at the section entitled "Addition of Corticosteroids At Progression of Abiraterone Acetate."

Previously you testified that four out of 11 patients responded to the combination of abiraterone acetate and dexamethasone where they had already progressed on dexamethasone and abiraterone acetate alone.

Do you remember that?

A. Yes.

Q. Were there any patients in the Dexamethasone Extension Study who had not received prior dexamethasone therapy?

A. Yes, that's the other group. So the Extension Study consisted of two groups, group 1 and group 2.

Group 1 was the group that we just talked about, which was the group that had dexamethasone previous, prior to abiraterone acetate; and then there was group 2, patients who had been -- who had never received dexamethasone prior to the abiraterone acetate. And that's, actually, a larger group. And those 19 patients and six out of 19 -- let me show it here -- responded, so 32 percent responded.

Q. Responded to what?

A. To the abiraterone acetate -- to the dexamethasone at the time of its addition to the abiraterone acetate.

MR. KRAUSE: If we could pull up PDX-4.66.

BY MR. KRAUSE:

Q. And if you recall, you were talking about differences or the alleged differences between the Attard 2009 and the Ryan 2011 studies. And with respect to the number of baseline lesions in patients, I believe you testified something like the lower number of patients with lesions favored Attard 2009 compared to Ryan 2011.

What did you mean by "favored"?

A. So baseline lesions is really a binary, yes or no, did they have metastasis or not?

In the Attard 2000 -- let me restart. In Ryan 2011, all of the patients, 100 percent, had metastatic disease. In the Attard 2009, 90 percent had metastatic disease and four patients had castration-resistant prostate cancer without detectible metastasis.

When I say "favor," those patients with metastasis are known to do better. So that if you take, all things being equal, a patient with metastatic CRPC, you patients with non-metastatic CRPC, are going to do better, they are going to live longer; they are going to have a better response to treatment; they'd have a longer time to PSA progression.

So, if anything, if you look at that population, it would make the time to progression data, the median data, longer in the Attard 2009 and bring them closer as compared to 100 percent of the patients -- if 100 percent of the patients in Attard 2009 had metastatic disease, all had metastatic, as opposed to a subset having non-metastatic.

Q. And can you remind us what the patients in Attard 2009 were treated with?

A. So the data here that we're talking about, are the data from abiraterone acetate and monotherapy.

Q. Okay. Doctor, I'd like to talk a bit more about inconsistent data or allegedly inconsistent data that the defendants raised.

I'd like to now talk about the defendants' argument that the 004 study found a lower time-to-PSA progression, than the 002 study recorded in Ryan 2011, which we discussed earlier, why is the median time to PSA progression in the 004 study lower than the 002 study published by Ryan 2011?

A. They're different populations. You remember what we talked about was prior chemotherapy being an important factor in the biology of the disease. So patients who've already had chemotherapy who are castration resistant have a more aggressive disease, one that's more intrinsically resistant to further treatments.

So the Ryan -- the 004 study, excuse me 004 study, is

a post-chemotherapy study. The 002 study is pre-chemotherapy. That's truly apples to oranges and you'd expect a shorter time to PSA progression in the 004 study as compared to the 002 study.

And, again, that was very well recognized and has been and continues to be well recognized, including by the FDA, and that's why they mandated a separate post-chemotherapy study for the phase III 301, and a pre-chemotherapy study, the phase III 302.

Q. So what does this indicate regarding whether the data are contradictory --

A. They're not.

Q. -- as defendants allege?

A. They're not.

Q. Are you aware that the defendants have also alleged the 003 study result suggest there is no difference in time to PSA progression between abiraterone acetate versus abiraterone acetate plus prednisone, in comparison to the results of the 004 study?

A. Yes.

Q. And what do you think of that?

A. So, I feel that that is inaccurate and the reason why is because, although the protocol for the 004 study -- so let me take a step back.

Both of those studies were post-chemotherapy

metastatic CRPC patients -- who were post chemotherapy.

The 004 study had written in the protocol that abiraterone acetate and steroids were to be used from the start. That wasn't actually written in the protocol of 003, but it turns out that patients were allowed to be on steroids and they were on steroids at the start of the abiraterone. So it's basically comparing apples to apples in that situation.

Q. So then why was the median time to PSA progression 120 days in both the 003 and 004 studies?

A. Similar populations post-chemotherapy CRPC patients.

Q. What does this indicate regarding whether the data are contradictory as the defendants allege?

A. They are not contradictory.

Q. Are you aware the defendants also argue that a few recent publications demonstrate that prednisone does not provide a survival benefit in the treatment of prostate cancer?

A. Yes.

Q. What experimental evidence do these publications provide that prednisone does not have an anti-cancer effect in combination with abiraterone acetate?

A. Absolute none.

Q. Why do you say that?

A. Those studies were meta analyses looking at randomized controlled trials and what they did was they isolated the arms that had prednisone only to ask -- in other words, control

arms, to ask the question whether or not prednisone might contribute to a survival advantage when it's administered by itself. And the conclusions, which I agree with, is that prednisone does not have an anti-cancer effect by itself.

It did not address -- those studies did not address the role of prednisone with abiraterone acetate, in combination. It was specifically pulling out the control arms with prednisone only.

Q. So what is your opinion of the relevance of those publications?

A. They're not relevant.

Q. Are you aware the defendants argue that Janssen's marketing materials show prednisone, as used by Zytiga, to mitigate side effects rather than for its anti-cancer effects?

A. Yes.

Q. What do you think of this argument?

A. I don't agree with it.

Q. Why is that?

A. So, first of all, every single marketing material has to have the indications and uses. So that's what we see. And as a physician, irrespective of what the remainder of the document demonstrates, we know what we're using it for. Okay?

Now, there are some materials that might emphasize survival and efficacy more than managing side effects, but all in all, they're very informative.

So even those that may focus on side effects and how prednisone may mitigate side effects, those are very useful, in my view, because once a physician decides I want to use abiraterone acetate and prednisone to treat prostate cancer, they then get information on how to manage the patients.

So it's really helping us manage patients safely. So it's doing -- giving information to the physicians and ultimately doing a service to the patients.

Q. Let's talk about the phase III trials of abiraterone acetate with prednisone. If you could turn to JTX-8091 in your binder.

A. Got it.

Q. Do you recognize this document?

A. Yes.

Q. And what is it?

A. This is the seminal publication of the 301 study, the randomized controlled trial of abiraterone acetate plus prednisone versus placebo plus prednisone in metastatic CRPC patients who had previously been -- had received docetaxel-based chemotherapy.

Q. And when was this published?

A. 2011.

Q. And where was it published?

A. The *New England Journal of Medicine*.

Q. What is the *New England Journal of Medicine*?

A. It's the most prestigious clinical journal there is, in my view, in the world. It is a general -- it publishes clinical manuscripts that are not restricted to cancer. It's really any field of medicine.

So the very fact that a cancer study is published here is recognized not only, of course, by the reviewers, but the editors that this is really important to get out to not only oncologists but medical community at large both in the U.S. and globally.

Q. Did you rely a JTX-8091 in forming your opinions?

A. Yes.

Q. And what was the name of the study described in the JTX-8091?

A. This is also known as the Cougar 301 or 301 study, and I believe it's study 1 in the updated version of the label.

Q. Is this the same 301 study described in the Zytiga label and defendants' labels?

A. Yes, it is.

Q. What patient population was analyzed in 301 study?

A. Metastatic CRPC after chemotherapy with docetaxel.

Q. And what drugs were administered in the 301 study?

A. Abiraterone acetate plus prednisone in one arm and placebo plus prednisone in the other arm.

Q. If you could please turn to Page 1996. Look at the last sentence of the first column.

A. Yes.
Q. It says there, We hypothesized that inhibition of androgen biosynthesis with abiraterone acetate and prednisone would improve survival among patients with advanced prostate cancer.
Do you see that?
A. Yes.
Q. What's being talked about there?
A. So this is just bringing out what I said earlier, that this study is now further moving along the combination and further establishing the hypothesis Dr. de Bono had postulated. And here we're looking at a regulatory endpoint, survival. So this is sort of the -- the -- the culmination of all the work that had been done previously.
Q. What is the most important metric for measuring the efficacy of an oncology therapy?
A. Ultimately, it's survival.
Q. What were the overall survival results in the 301 study?
A. They favored the -- they showed that abiraterone acetate and prednisone improves overall survival compared to the control arm in a clinically meaningful and statistically significant manner.
Q. And so how many months did the individuals in the treatment arm live, on average?
A. Those -- about a four-month difference total with a hazard ratio of 0.65. Meaning a 35 percent reduction in the risk of

dying at any point, in the combination arm, with abiraterone and prednisone, and this was highly statistically significant with a P value less than 0.001.

Q. So at a high level, what's your takeaway from this reference?

A. The combination of abiraterone acetate and prednisone improve overall survival in metastatic CRPC patients who've had docetaxel.

Q. How, if at all, does 301 study relate to the asserted claims?

A. So the -- it involves the same drugs, abiraterone acetate and prednisone, at the precisely same dosages in the same patients with the same disease. So it really matches up very well.

Q. When did Zytiga with prednisone first receive FDA approval?

A. April 2011.

Q. If you could turn to JTX-8104 in your book.

A. Got it.

Q. Do you recognize JTX-8104?

A. Yes.

Q. What is it?

A. This is the pre-chemotherapy phase III study that was involving abiraterone acetate plus prednisone versus the control arm in patients with metastatic CRPC who had not yet

received docetaxel.

Q. Where was this published?

A. Same journal. *New England Journal of Medicine*.

Q. Did you rely a JTX-8104 in forming your opinions?

A. Yes.

Q. If you could turn to Page 139 and look at the second sentence in the paragraph at the bottom of the first column.

A. I'm sorry the second paragraph?

Q. In the paragraph at the bottom, the first column?

A. Yes.

Q. The sentence states, Abiraterone plus low dose prednisone improves survival in patients with metastatic castration-resistant prostate cancer who have already received docetaxel and the combination therapy has received regulatory approval for this indication.

As a physician, what's your understanding of that sentence?

A. It's a reiteration of the 301, the primary 301 results that we just discussed. And that is the combination of abiraterone acetate and prednisone, that improves survival in patients with mCRPC who have received chemotherapy and that combination was FDA approved.

Q. If you could turn to JTX-8108 in your binder.

Do you recognize this document?

A. I do.

Q. And what is it?
A. This is the final survival analysis of the study that we just discussed, the 302 study. And this is a study that is further confirming the survival advantage and it's published in a journal called *Lancet Oncology*, another prestigious specialty journal. Oncology specialty journal.
Q. Did you rely on JTX-8108 in forming your opinions?
A. Yes.
Q. Is this the same 302 study described in the Zytiga label in defendants' ANDA labels?
A. Yes.
Q. What patient population was analyzed in the 302 study?
A. Men with mCRPC who have not yet received docetaxel.
Q. How do the patient populations in the 301 and 302 studies compare?
A. They both have mCRPC. 301 is post chemo and 302 pre-chemo.
Q. And what drugs were administered in the 302 study?
A. Abiraterone acetate and prednisone in one arm and placebo and prednisone in the other arm.
Q. What was the overall survival results of the 302 study?
A. So the median overall survival was 34.7 months in the combination arm and 30.3 months in the control arm.
And please remember that the patients in the control arm had been offered abiraterone acetate at the first interim

analysis because the data safety monitoring board that oversaw this study felt that it was not ethical to allow patients to remain on the placebo plus prednisone arm.

So what that's telling us is that this survival advantage can be dampened because of this un-blinding process.

Q. How did the 302 results relate to the asserted claims?

A. They matched very well. Same patients, same dosages of drugs, same disease.

Q. If you could turn to Page 159 and look at the first sentence under the heading "Interpretation."

The sentence states, The final analysis of the COU-AA-302 trial demonstrates that abiraterone acetate plus prednisone prolongs overall survival compared with placebo plus prednisone in patients with chemotherapy naive metastatic castration-resistant prostate cancer.

As a physician, what's your understanding of that sentence?

A. That just is establishing the gold standard for improvement in an outcome, overall survival in the patients who got the experimental arm of abiraterone acetate and prednisone.

Q. Did Zytiga with prednisone receive an FDA approval after the 302 study?

A. Yes.

Q. And when was that?

A. December 2012.

Q. In the 301 and 302 studies, prednisone was administered in both the treatment arm and the control arm. Is that correct?
A. Yes.
Q. What does the 301 and 302 study design allow you to conclude about the anti-cancer effects of abiraterone acetate with prednisone?
A. I conclude that abiraterone acetate and prednisone are working together to achieve the clinical treatment effect, the anti-cancer effect.
Q. Can the effects of prednisone in the control arm simply be subtracted from the benefits of abiraterone acetate and prednisone in the treatment arm to show that abiraterone acetate has an individual anti-cancer effect?
A. No.
Q. Why is that?
A. So when drugs are combined, there can be different outcomes. They can be additive, they can be antagonistic or they can be greater than additive. The biostatistical term is synergistic. And we've already established that the combination is greater than additive. As an example, you can go back to the extension study as a good example of that.
Q. Are you familiar with the LATITUDE study?
A. I am.
Q. What is the LATITUDE study?
A. That was a randomized control trial of patients with

metastatic castration-sensitive prostate cancer and all patients received androgen deprivation therapy; and the question was asked, can we add abiraterone acetate and prednisone at the start of treatment for metastatic CSPC and will that -- to achieve an improvement in clinical outcomes.

Q. Could you please turn in your binder to PTX-22.

A. Got it.

Q. Do you recognize PTX-22?

A. This is the LATITUDE study.

Q. Did you rely on PTX-22 in forming your opinions?

A. Yes.

Q. What patient population was evaluated in the LATITUDE study?

A. These are the metastatic castration-sensitive prostate cancer patients.

Q. Are these the newly-diagnosed patients?

A. Yes. Well, they're newly -- they're newly going on hormone therapy.

It is possible that they had a diagnosis of localized prostate cancer many years ago and then the cancer came back as metastatic. But they are naive to castration, let's put it that way.

Q. How is that patient population different from mCRPC patients?

A. So mCRPC patients have had castration and then manifested

some measure of the cancer getting worse, disease progression.
Q. What drugs were administered in the LATITUDE study?
A. So all patients, in both arms, were required to receive castration and then one arm, the experimental arm, received abiraterone acetate and prednisone and the other arm got matched double placebos.
Q. Why wasn't prednisone administered in the placebo arm of the study?
A. So these patients, in general, are going to do better because they're newly diagnosed. They haven't been -- become castration resistant. So just being on androgen deprivation therapy alone will provide a long-term benefit before the cancer gets worse.

So if you put a patient on a corticoid steroid in the control arm, what you're going to do is the patient will stay on it so long as they don't progress and that can be years.

So we know about the chronic toxicities of prednisone and it was felt that it wouldn't be -- it would not do the patients a service to put them on prednisone. I think that's a dominant factor.
Q. What were the overall survival results of the LATITUDE study?
A. Overall survival was improved in the experimental arm containing abiraterone and prednisone.
Q. What is the significance of the LATITUDE study results to

you as a treating physician?
A. It was practice changing, as were the 301 and 302 studies.
Q. Why do you say that?
A. Because the survival advantage that we saw with the combination of abiraterone acetate was so striking and it was so well-tolerated that, essentially, any patient that fits the criteria in the label can be now treated with abiraterone acetate and prednisone, when they first start castration, to achieve a meaningful clinically impactful improvement in quantity of life.
Q. How does the use of 1000 milligrams per day of abiraterone acetate and 5 milligrams per day of prednisone to treat mCRPC relate to asserted claim 4?
A. It does. It identifies -- so claim 4 is all about abiraterone acetate dosage of 1000 milligrams per day, and that's the same dosage that's in -- that was in the study.
Q. If you could turn to Page 2 of PTX-22 and look at the third sentence beginning, Abiraterone acetate, in the second column.

The sentence states, Abiraterone acetate, hereinafter referred to as abiraterone, in combination with prednisone, has been shown to significantly increase overall survival and provide additional clinical benefits in patients with metastatic castration-resistant prostate cancer who have not received chemotherapy and in those who have received previous

docetaxel.

What's your understanding of that sentence?

A. This is just summarizing, briefly, the results of the two previous randomized control trials in the castration-resistant state and calling out, specifically, abiraterone acetate in combination with prednisone, highlighting that fact.

Q. If we could turn to Page 1 of PTX-22 and look at the sentence under the heading "Conclusions."

The sentence states, The addition of abiraterone acetate and prednisone to androgen deprivation therapy significantly increased overall survival and radiographic progression-free survival in men with newly-diagnosed metastatic castration-sensitive prostate cancer.

What's your understanding of that sentence?

A. Again, it's a reiteration of the results where abiraterone and prednisone, when added to ADT, are improving these clinical endpoints, overall survival, and something called radiographic progression-free survival, which means either scans get worse or patients die.

Q. Did Zytiga with prednisone receive an FDA approval after the LATITUDE study?

A. Yes.

Q. And when was that?

A. That was February 2018.

Q. What relationship did the Attard 2009 and Ryan 2011

studies have with the phase III Zytiga trials?
A. They were the foundation, the basis for their development. They confirmed the de Bono hypothesis. They established that abiraterone acetate and prednisone are functioning together to achieve their combined clinical effect, and this was ultimately manifested in the overall survival advantage in these three clinical randomized controlled clinical trials that we just discussed.
Q. Dr. Rettig, based on all of this information, what is your opinion with respect to prednisone's anti-cancer effect in combination with abiraterone acetate?
A. My opinion is that it has a real contribution to the overall anti-cancer effect of abiraterone when it is prescribed with prednisone.
MR. KRAUSE: Thank you, Doctor.
I pass the witness.
THE COURT: All right. Who will be crossing?
MR. KLEIN: I will.
CROSS-EXAMINATION
BY MR. KLEIN:
Q. Good afternoon, Dr. Rettig.
A. Good afternoon. You're Mr. Klein, correct?
Q. Yes. I was going to just introduce myself.
My name is Charles Klein, with the law firm of Winston & Strawn, and I will obviously be asking you some questions on

behalf of defendants.

You can keep that binder. We handed you another binder. We'll, obviously, be putting documents on the screen and whatever is easier for you. The pertinent pages will be on the screen, but if you want to look at the actual documents, that's perfectly fine. Okay?

MR. KLEIN: Mr. Russell, can you put up PDX-4.3, please. PDX-4.3.

BY MR. KLEIN:

Q. Dr. Rettig, do you recognize this slide from your direct examination?

A. Yes.

Q. Okay. And this slide reflects how counsel instructed you on some of the legal principles in this case, right?

A. Yes.

Q. And did counsel instruct you that defendants' abiraterone labels do not induce or contribute to infringement unless the FDA has approved the patented use?

A. No, that's not my understanding.

Q. Okay. Do you understand that a key issue in this case is whether the FDA has approved prednisone to achieve anti-cancer effects when prednisone is used in combination with abiraterone? Is that an understanding you have?

A. Yes. However, my understanding for infringement is that it's the practice of what's in the patent, the claims.

Q. Okay. So do you have an understanding one way or another as to whether the specific scope of FDA approval is related to whether defendants infringed the patent?
A. Yes.
Q. Okay. All right.
Now, you understand that FDA has detailed regulations that govern the approval of drugs just generally, right?
A. Yes.
Q. Okay. And you're not an expert in FDA regulations, correct?
A. No.
Q. You're not an expert in FDA approvals?
A. No. I have a working knowledge, but not an expert.
Q. You don't read FDA regulations. That's not something you typically do, right?
A. No, not typically. I have read some, yes.
Q. And you're certainly not an expert in the regulatory requirements that are required by the FDA to approve a New Drug Application, correct?
A. Not an expert.
Q. You never worked at the FDA?
A. No.
Q. You never served on any FDA committees responsible for approving an indication for a New Drug Application, right?
A. No.

Q. And you never served on any FDA committee responsible for reviewing clinical trials, right?
A. No.
Q. You're not an expert in clinical trial design, right?
A. I have a pretty good working knowledge of clinical trials. I wouldn't say I'm an expert. I do design clinical trials, write protocols, in combination with other experts.
Q. Okay. You're not an expert in biostatistics, right?
A. No.
Q. And you're not an expert on labelling for human prescription drugs, right?
A. Not an expert.
Q. And you have no training on the requirements for FDA labelling, right?
A. No formal training.
Q. Okay. And you've never drafted an FDA-approved indication, right?
A. I've never drafted a label.
Q. And so you don't offer any opinion in this case on the issue of whether FDA has approved prednisone for anti-cancer effects, in combination with abiraterone, correct?
A. No. I have offered my opinion as a physician, a person of ordinary skill who has knowledge of the field, right.
Q. That's my next question. Okay.
So your testimony about the Zytiga indication is

solely from the perspective of a clinician, right?
A. Yeah, as a physician with knowledge of the field.
Q. Okay. And you understand that -- you talked about on-label and off-label uses a little bit on your direct, right?
A. Yes.
Q. Okay. You understand that pharmaceutical companies -- you generally understand -- I'm not going to ask any specifics -- you generally understand that pharmaceutical companies can't market a drug for an off-label use, right?
A. Yes.
Q. But doctors are not bound by the scope of a FDA drug indication, right?
A. That's my understanding.
Q. Doctors can describe for use even if FDA hadn't approved it?
A. That's possible.
MR. KLEIN: Can we go to DDX-2701.03, please.
BY MR. KLEIN:
Q. Okay. On the screen, you recognize this as the 2018 Zytiga label?
A. Yes.
Q. Okay. And this Zytiga label, the indications and usage section, in particular, never actually tells doctors that prednisone is indicated to achieve anti-cancer effects, correct?

A. No, that is not correct.
Q. And so are you testifying that this Zytiga indication -- and for the record, it's DTX-1580.2 -- encourages doctors to use prednisone for anti-cancer effects; that's your testimony?
A. Yes.
Q. But you have personally told doctors that the role of prednisone in the Zytiga indication is for safety, correct?
A. No, that's false.

I have told doctors that the role of prednisone is for its anti-cancer treatment effect. It has an added benefit of potentially mitigating side effects, but that's not its role. That's not its primary role. That's not why it is administered.

Q. Okay. On direct you talked about how you served on Janssen's speakers bureau, right?
A. Correct.
Q. Okay. And in that capacity, you specifically talked to doctors about the Zytiga drug, right?
A. In combination with prednisone, yes.
Q. Right. You gave more than 20 speeches about Zytiga, roughly speaking?
A. Yes.
Q. And for these speeches, in total, Janssen has paid you about $100,000, right?
A. Something like that.

Q. And you understand that FDA had to approve the marketing slides you used and the notes for the Zytiga speeches, right?
A. They approved the slide deck and any material that was used.
Q. And because these are -- these were FDA-approved presentations, you had -- your prepared speeches had to stick to the FDA-approved slides, right?
A. Yes, unless I received an unsolicited question, and I can respond to that.
Q. Okay. And during these presentations, you told doctors that prednisone is used with Zytiga to address side effects, right?
A. No. I'll repeat. The main reason that I used -- that I -- what I principally indicated to the -- to the audience was that the main reason and the driving reason that prednisone is being used with Zytiga was for its anti-cancer effects.

There was a secondary role related to safety, where we have this added benefit that prednisone helps to mitigate side effects from abiraterone acetate.
Q. Okay. So during these speeches, you were telling doctors that safety was only a secondary role for prednisone?
A. Yes. The primary role is for the treatment of prostate cancer in combination with abiraterone acetate.
Q. Okay. Are you saying -- so did -- as a physician, as a clinician -- not as an FDA person, but as a clinician, are you

saying that this indication is not telling doctors to use prednisone for safety, only efficacy?

A. Yes, that's what I'm telling you.

MR. KLEIN: Let's go to DDX-2701.4. And the document is DTX-1697.1.

BY MR. KLEIN:

Q. Do you recognize this as a Zytiga slide deck you personally presented to doctors?

A. Yes.

Q. And this slide deck came from Janssen, right?

A. Yes.

Q. And you understood that it was FDA approved?

A. Yes.

Q. And you see the date is July 2016?

A. Hmm-hmm -- yes.

MR. KLEIN: Let's go to DDX-2701.5.

BY MR. KLEIN:

Q. Okay. Here's -- this is obviously the notes version of a PowerPoint, but this slide addresses the 302 clinical trial design, right?

A. Yes.

Q. And your notes have some bullet points under the heading "Key Points."

Do you see that?

A. Hmm-hmm.

Q. You have to say "yes" or "no" for the record.
A. I'm sorry. Yes.
THE COURT: Sorry. I know it does -- it sounds a lot like "huh-uh."
THE WITNESS: I apologize. Yes.
BY MR. KLEIN:
Q. Okay. And the last bullet, which is highlighted, says, Co-administration with prednisone, and it's talking about co-administration of abiraterone with prednisone, right?
A. Yes.
Q. A corticosteroid suppresses ACTH, resulting in the reduction in the incidence and severity of mineralocorticoid-related adverse reactions, right?
A. Yes.
Q. And this is a fancy way of saying prednisone reduces abiraterone side effects, right?
A. Yes, but I don't think -- we can't ignore -- not only the other key points on this slide, but other key points throughout the whole slide deck that emphasize the initial results, the efficacy results. That's what's presented first and foremost. And if you look here --
Q. But, sir -- sir, your counsel will have a chance for redirect.
But just to be clear, there's nothing in this slide deck that says prednisone is having anti-cancer effects. I'm

not talking about the combination.

There's nothing in your slide deck that says prednisone itself is having anti-cancer effects, correct?

A. No, that's incorrect.

Q. Okay. Well, if I'm incorrect, your counsel can correct me on redirect.

A. Can I please clarify that?

Q. That's what redirect is for, sir.

Prednisone -- prednisone has been used -- at the time you were making this speech to doctors, prednisone had been used, with other cancer drugs, for similar purposes, right?

A. No, that's incorrect.

Q. For palliation?

A. Historically, I would say many years ago prednisone had been used for specific palliative purposes in the prostate cancer management world. And prostate cancer has some unique complications, especially bone pain, that we could have used prednisone for palliation.

However, patients who go on these clinical trials are living a long time. Remember, the control arm in the 302 study lived 30 months.

So putting that patient on prednisone for some bone pain would subject that patient to the remaining of his life with all of the toxicities of prednisone. And we have such better ways of palliating the symptoms that we used to use

prednisone more readily for.
Q. Okay. You understand Zytiga's initial approval was in 2011, right?
A. Yes.
Q. Okay. In 2011, steroids like prednisone had been approved for glucocorticoid replacement therapies, right?
A. I believe so, yes.
MR. KLEIN: Let's go to DDX-2701.6.
BY MR. KLEIN:
Q. This slide is called Steroidogenesis Pathway, Co-Administration of Prednisone, right?
A. Hmm-hmm.
Q. I'm sorry --
A. I'm sorry, I keep doing that. It's my colloquial way of responding. Yes.
Q. Okay. This side is a bit complicated for us nonmedical folk, but the key point is that prednisone is addressing abiraterone side effects, right?
A. No, I would not say that's the key point. There are several key points here, if I can point them out to you.
Q. Okay.
MR. KLEIN: Well, let's just go to the next slide, DDX-2701.7.
BY MR. KLEIN:
Q. These are the notes to the slide we just looked at, and

you see there's one key point in the notes. Do you see that?
A. I see that. These key points -- so let me just take a step back --
Q. Well, sorry. The way cross-examination works is I ask you the questions, you answer it. If there's additional explanation, your counsel can come up and ask you to clarify it.
A. I see.
THE COURT: Within reason.
MR. KLEIN: Within reason.
BY MR. KLEIN:
Q. The key point, the notes of this slide say the key point is that co-administration of a corticosteroid suppresses adrenocorticotropic hormone drive resulting in a reduction in the incidence and severity of the adverse reactions of hypokalemia, hypertension and fluid retention, right?
A. That's what it says, yes.
MR. KRAUSE: Your Honor, if I can I object, because we don't have copies of these demonstrative exhibits.
MR. KLEIN: Your Honor, they came from Janssen. They were produced from Janssen to us.
THE COURT: Well --
MR. KRAUSE: Well, he is selecting which pages --
THE COURT: Look, I'm just going to guess that these are among a large volume of material. Help him out. Let's --

MR. KLEIN: I have -- the document number is DTX-1697.66. This was a production Janssen made to us.

THE COURT: Okay.

MR. KRAUSE: Your Honor, we had DDX numbers on here. Apparently, he has a stack of these things. I think it would be appropriate for us to have a copy of them.

As he pointed out, this is amongst the stack of the entire production. We don't know what's coming up next.

MR. KLEIN: I think they're asking for our demonstrative for cross-examination? Is that what you're asking for?

MR. KRAUSE: Yes.

MR. KLEIN: That's highly unusual, in my experience, that you give demonstratives for cross-examination. We have not --

THE COURT: I'm not sure what "demonstratives for cross-examination" even means.

MR. KLEIN: These are documents -- and I gave the wrong number -- it's DTX-1697.

And I think what counsel is saying is we should have told him that we were going to cross their witness on this document, which is highly unusual.

MR. KRAUSE: No, Your Honor, we simply --

THE COURT: I think he is asking for it now.

MR. KRAUSE: Yes.

MR. KLEIN: You didn't give him a binder? The binder has the documents. He wants the slides?

MR. WONG: Yes.

MR. KLEIN: Okay. Give him the slides.

THE COURT: Let him see it. Let him follow up. He's not making a discovery objection. He's just saying he wants to have it in front him.

MR. KLEIN: I misunderstood.

THE COURT: Okay.

BY MR. KLEIN:

Q. All right. I think I read into the record what the key point is, as indicated in the notes of slide 65 of DTX-1697. All right.

All right. In essence, this key point -- again, it's a little complicated. It's saying, Coadministration of a corticosteroid like prednisone addresses abiraterone side effects.

That's what the notes are saying, right?

A. That's what the notes are saying.

Q. Now, to your knowledge, the FDA has not allowed Janssen to tell doctors that prednisone has anti-cancer effects when used with Zytiga, correct?

A. Incorrect.

Q. Other than citing the "indications" section, your slide presentation never actually says that prednisone has

anti-cancer effects in combination with abiraterone to improve overall survival, correct?

A. Incorrect.

MR. KLEIN: Mr. Russell, can you play deposition 1, Pages 344 to 345, starting line 3 of 344 to line 3 of 345?

(Video of Deposition 1 of Matthew Rettig is played.)

Q. Is that your testimony, sir?

A. That is a component of my testimony. That doesn't completely recapitulate what I said in that testimony.

Q. Now, FDA has not approved discussions of anti-cancer effects from prednisone when used with Zytiga, to your knowledge, correct?

A. I'm sorry, repeat the question.

Q. Let me rephrase it.

You talked about a mechanism of action of how prednisone might contribute to overall efficacy of the combination with Zytiga, right?

A. I have spoken about that, yes. Yes.

Q. That discussion is not part of the FDA-approved presentation material, correct?

A. The FDA-approved presentation material does not specifically call out that mechanism of action whereby prednisone potentiates the effects of abiraterone acetate and how they would work together to achieve an anti-cancer effect.

Q. Okay. Thank you.

Now, you testified earlier that, in your view, the Zytiga indication --

THE COURT: I'm sorry, just one other thing, just because it was raised before.

When we say "FDA approved," was it pre-approved? It doesn't have to be, right?

THE WITNESS: So, my understanding, Your Honor, is that the slide deck is approved by the FDA.

THE COURT: Before you delivered?

THE WITNESS: Yes, sir.

THE COURT: The presentation. Okay, thanks.

MR. KLEIN: Your Honor, I think you're referring to testimony about Janssen's marketing materials.

THE COURT: Marketing material, yes. And I just wondered if this was pre-approved or not.

BY MR. KLEIN:

Q. Now, when we talked about the indication and you said the indication is saying prednisone has anti-cancer effects, am I correct, that's your view?

A. Yes.

Q. Okay. Is that because the Zytiga indication is phrased in a way that says take Zytiga, in combination with prednisone, to treat patients with prostate cancer?

Is that wording, in your view, expressing to a doctor that prednisone has anti-cancer effects?

A. Yes, in isolation, but as a physician, I would use the whole body of information that I have to make that determination. And I have determined that prednisone, indeed, functions in combination with abiraterone acetate to achieve its anti-cancer, prostate cancer effect.
Q. And when you say "the whole body," you're referring to, among other things, the 001 study, right?
A. 001, 002, 003, 004, the 301, 302 studies and the LATITUDE study as well.
Q. Now, we talked a moment ago about the fact that before Zytiga was approved, prednisone was used with other cancer drugs, right?
A. Yes.
Q. And one of those drugs is called Jevtana?
A. Yes.
Q. All right.
MR. KLEIN: Let's go to DTX-2701.8.
BY MR. KLEIN:
Q. Do you recognize DTX-1282.1 as the Jevtana indication and usage section?
A. Yes.
Q. Okay. And you see it says, Initial U.S. approval 2010?
A. Yes.
Q. So this is about a year before Zytiga was first approved, right?

A. Yes.
Q. Okay. And you personally prescribed Jevtana?
A. Yes, I have.
Q. And the Jevtana label says that the drug -- now I'm paraphrasing, but it's indicated, in combination with prednisone, for the treatments of patients with a form of prostate cancer, right?
A. Yes.
Q. Right.

MR. KLEIN: Now, let's go to DTX-2701.9.

BY MR. KLEIN:
Q. And here is -- we've got the Zytiga label on the top, which is DTX-1580.2, and the Jevtana label from 2010 on the bottom, DTX-1282.3.

Do you see that?
A. Yes.
Q. Okay. And, generally speaking -- I mean, there are some specifics that are different, but, generally speaking, the phraseology is similar between the two indications, right?
A. Yes.
Q. And your opinion is that prednisone is not providing an anti-cancer effect, according to the Jevtana indication, correct?
A. So let me explain. When one looks at these labels in isolation, if one does not have any medical knowledge and just

reads the labels, one would conclude in this artificial way, perhaps in a regulatory or legal way, that prednisone does contribute to the anti-cancer effect of Jevtana.

As a physician, when I look at a label, I don't look at it in isolation. I look at it in the context, as I said, of everything I know. And what I know, is that I have never seen a hypothesis that prednisone contributes to the anti-cancer effect of Jevtana, I've never seen a clinical trial that even tried to establish such a hypothesis, which I didn't see in the first place, such as an extension study.

So when I look at the Jevtana label in the context of what I know, as opposed to the Zytiga label, I, as a physician, in my -- make different conclusions.

Q. And so I'm not sure you answered the question directly, but I understand your answer.

But your opinion is that prednisone is not providing an anti-cancer effect when used with Jevtana, correct?

A. Yes.

Q. Okay. And you explained how physicians look at -- look at more than just the indication and usage section, right?

A. Yes.

Q. Okay. They read the label as a whole, correct?

A. Yes.

Q. And then they may look at information outside the label as well, right?

A. Sure, yes.
Q. And there was -- there's nothing in the Jevtana label that would convince a physician that prednisone's having an anti-cancer effect, right?
A. Correct.
Q. Okay. And for Zytiga, you're saying that, as a physician, you are aware of the 001 study that had this reversal of resistance to abiraterone hypothesis, correct? Is that the distinction between Zytiga and Jevtana, in your mind?
A. That's one distinction.
Q. But that's the key distinction, though, right?
A. It is a key distinction. There are other key distinctions.
Q. Okay. You understand that the 001 study is not reported in the Zytiga label, right?
A. Yes, I understand that, but one can and one would normally, as a physician, look at the clinical trial section, get the papers, and then be referred to those papers.
Q. Okay. So in your opinion, a physician would look at the clinical trial section of Zytiga and then do some digging, pull the studies and, eventually, come across the 001 study; is that what you're saying?
A. Yes, and would do the same for Jevtana.
Q. Okay. And then the difference between the two drugs is that if you did that for Jevtana, you're not going to find

something like the 001 study?
A. The 001 study and all of the other studies and work that had been done with Zytiga.
So there were no analogous studies that were done for Jevtana and no analogous hypothesis.
Q. Okay. And so I'm not sure we clarified this, but when doctors use Jevtana with prednisone, they're using prednisone for palliation; is that right?
A. No, not quite. The Jevtana is called -- is the brand name for a chemotherapy agent Cabazitaxel. It sounds like docetaxel, because they belong to the same class called taxane. And taxanes have a very unique and very serious life-threatening acute side effect. It's called a hyper-sensitivity reaction. In fact, there's a black box warning in those labels and there's a requirement for physicians to prescribe super-high dosages of glucocorticoids.
Within the 12 hours prior to receiving the chemotherapy, patients must have received the equivalent of 171.6 milligrams of prednisone and then they stay on the prednisone throughout each cycle.
Q. You can't tell that role of prednisone from reading the Jevtana indication, right?
A. No, but it's -- the black box warning is first and foremost on the label.
Q. And so, I'm not sure I understand. What exactly is the

role of prednisone when used with Jevtana?
A. Sorry, we'll get back to that?
Q. Yeah.
A. I forgot the question.
So prednisone is largely to mitigate the side effects of Jevtana. That's different than palliation. Palliation refers to the disease.
Q. Okay. Is that your understanding, as a physician, as to why FDA approved Jevtana in combination with prednisone?
A. So my understanding is that the FDA approved Jevtana in combination with prednisone for its anti-cancer effect and that's what's in the label in the indications and usage section. That's different from what I, as a physician, understand the role of prednisone.
Q. Okay. And that understanding of what FDA did, is that just from reading the indication and usage section or is that from some other information?
A. It's from the indications and usage section and the FDA has used the phase III study as an important component of their decision to approve that combination.
Q. Okay. But certainly doctors would look at the Jevtana indication today with knowledge of, you know, the label as a whole and other information and read that indication as saying Jevtana is indicated in combination with prednisone because prednisone is going to address Jevtana side effects, correct?

A. No, that's not what I said. I said that the label says that they are supposed to be used in combination.

The doctor would read the indications and usage section, if you want, in isolation, that's what it says; that prednisone is being used with Jevtana for its anti-cancer effect.

The premise that I'm trying to get across, is that a doctor wouldn't use just the indications and usage section of any label to have a fulsome understanding of the therapy that they are considered.

Q. I think we are saying the same thing. I think I may have asked the question poorly.

A doctor looking at the Jevtana label as a whole, including the indications and everything else in the label, would read the indications in context as saying, prednisone should be used with Jevtana for side effects not as a second anti-cancer agent, correct?

A. Yeah, I think -- what I'm trying to say is, we don't just look at the indications and don't just look at the label as a whole. We look at everything else: We use our training, our experience and the literature.

So when you have a label in front of you, that's not the only source of information that a physician uses, especially when we are talking about patients who have life-threatening illnesses, and we're talking about drugs that can

have severe toxicity, chemotherapy.
Q. And I totally understand that.
So when you're offering opinions about what the Zytiga label as a whole is teaching to a doctor, you can't isolate that question from what a physician would know from the literature as well and everything else the doctor would know about the drugs, right?
A. Well, I can isolate it hypothetically, but I'm telling you how the mind of a physician works; how I would look at the label.
Q. I see. And so can you isolate, hypothetically, how a doctor would read the Jevtana label as a whole, not just the indication, the Jevtana label as a whole?
Would a doctor read just that label, if he or she picked up the label, had no other information, and be taught that prednisone is being used for anti-cancer effects?
A. So we have no other knowledge and we just look at the label, yes, what that says is that the combination of abiraterone acetate and prednisone both contribute to the anti-cancer effect.
Q. But you're saying a doctor wouldn't rely just on that, probably because there's nothing in the label that specifically says that other than the indication, correct?
A. No, the clinical trials support that as well.
Q. The clinical trials in Jevtana?

A. I'm sorry, which label are we talking about?
Q. Jevtana. We're still talking about Jevtana.
THE COURT: Let's back up. I think he answered the last question in respect to the abiraterone label, right?
THE WITNESS: Yes.
Q. Okay. Sorry for the confusion.
Let's talk about Jevtana. You said hypothetically you could isolate just the label. Okay.
So you have a doctor picking up the Jevtana label, reading the indication, reading the label as a whole. Would that doctor believe that prednisone is being used for anti-cancer effects, or to determine the role of prednisone in the Jevtana label would the doctor have to go outside of the label?
A. Looking at the label, hypothetically, pretend world, looking at the Jevtana label without any other information or knowledge, experience, training, et cetera, one would conclude, from looking at the Jevtana label, that is the combination of Jevtana plus prednisone, in the combination, that achieves the anti-cancer effect.
Q. And that's because of what, the indication and usage section?
A. And the clinical trial section.
Q. Of Jevtana?
A. Correct.

Q. What is it in the clinical trial of Jevtana that teaches that prednisone has anti-cancer effects? I'll strike the question.

Can we agree that, based on the indications for Jevtana and the clinical trials that support it, a doctor would not understand that both Jevtana and prednisone are contributing to the overall survival of patients taking the combination?

A. Are you referring back to the hypothetical?

Q. Well -- okay. Let me -- so here is the hypothetical:

A doctor only has this label in front of him, the Jevtana label. Based on the indications and usage of Jevtana and the clinical trials that support it, would a doctor understand that both Jevtana and prednisone are contributing to the overall survival of the combination?

A. Looking at the Jevtana label only and incorporating no other information but the label in its entirety, a doctor would conclude that Jevtana and prednisone both contribute to the anti-cancer effect of Jevtana.

Q. Let's take a look at another label. DDX-2701.10.

Do you recognize this as the Taxotere label?

A. Yes.

Q. This label is older. It's from May 2004, right?

A. Yes.

Q. And you're familiar with this because it's prior art,

right?
A. Yes.
Q. We discussed this label briefly, without an exhibit, on direct examination, right?
A. Yes.
Q. And Taxotere is obviously a cancer drug?
A. Yes.
Q. Okay. And the indication for Taxotere says, Taxotere, in combination with prednisone, is indicated for the treatment of patients with a form of prostate cancer, right?
A. Yes.

MR. KLEIN: Now, let's go to DDX-2701.11.

BY MR. KLEIN:
Q. Okay. Now, on the screen I've got three separate indications that I'll walk through them briefly.

On the top we have the 2018 Zytiga label again, and that's DTX-1580.2.

In the middle we have the 2004 Taxotere label that we just looked at, and that's DTX-1278.17.

And on the bottom we have the 2015 Taxotere label, which is DTX-1288.3, right?
A. Yes.
Q. Okay. And so the -- you understand the Taxotere label was eventually amended?
A. Yes, I think I understand that.

Q. Okay. But it's substantively identical, correct?
A. Yes.
Q. Okay. And both of the indications for Taxotere and Zytiga similarly say that the drug is indicated, in combination with prednisone, for the treatment of patients with a form of metastatic prostate cancer, right?
A. Similar form, yes.
Q. Okay. In your view, the Taxotere indication doesn't encourage doctors to use prednisone for anti-cancer affects, right?
A. So the entire conversation we just had for Jevtana applies to Taxotere. We can go through it again. I'd be happy to.
Q. And you're saying doctors don't look at the indication as a whole, right?
A. We look at the indication as a whole, we do.
Q. I misspoke. You're saying doctors don't look at the indication in isolation, right?
A. That's correct.
Q. And the Taxotere label doesn't say that prednisone is being used for anti-cancer effects, correct?
A. No, that's not what the label says in isolation. The label says that Taxotere is being used in combination with prednisone for the treatment of patients with a form of prostate cancer.
Q. Okay. Just to make sure I understand this. Are you

saying that the 2004 Taxotere label, as a whole, is teaching those skilled in the art that prednisone is being used for anti-cancer effects, in combination with Taxotere?

A. So it's going to go back to whether we're talking about real world or hypothetical. Which answer would you like?

Q. Well, I'd like you to focus on just the label.

A. Okay.

Q. Because for infringement we're focusing on the label.

A. Okay.

Q. Okay. So if -- are you saying that the 2004 Taxotere label, including the indication, is teaching doctors that prednisone is being used for anti-cancer effects when used with Taxotere?

A. Yes.

Q. And that's because of how it's worded?

A. How it's worded and that's what's in the clinical trial section. The FDA approved it based upon the clinical trial -- in part, on the clinical trial section.

Q. But it's your opinion that a doctor would understand -- in the real world, a doctor would understand that prednisone, in the Taxotere indication, is not being used for anti-cancer effects, correct?

A. Yes. The same analogy, same concept that I applied to Jevtana applies to Taxotere, yes.

Q. And the key distinction between Taxotere and Zytiga, in

terms of the labels or in terms of the drugs, is that Zytiga came from the 001 study and Taxotere didn't have a similar type of study to assess anti-cancer effects, correct?

A. That's a little bit of it. That's just a part of it. They're completely different drugs.

Q. I want to focus on the role of prednisone in the Zytiga label versus the role of prednisone in the Taxotere label.

I totally understand that Zytiga and Taxotere are very different drugs.

A. Okay.

Q. I just want to focus on the role of prednisone. And if I understand correctly, you're saying a doctor, today, in the real world, using Zytiga, would understand prednisone is for anti-cancer effect; but a doctor, in the real world, looking at using Taxotere, would understand prednisone is just for safety, right?

A. Yes.

Q. Okay. And the reason that there's this distinction is because of the 001 study, correct?

A. Again, that's part of it. There's other studies. There's actually no rationale, no hypothesis that's ever been put forth that prednisone would collaborate with Taxotere or Jevtana, for that matter, for its anti-cancer effect.

So that's just one part of it is 001. That's one, I would say, really neat study that helped establish the de Bono

hypothesis, but there's a lot else.
Q. And just to be clear, that de Bono hypothesis is in the 001 study, right?
A. Yes, that's -- that's built into the 001 study.
Q. So if you didn't have the 001 study, then we'd be in the same position, with regard to the role of prednisone, for Zytiga and Taxotere, correct?
A. Incorrect.
Q. What other study?
A. So we have the hypothesis and then we have the other studies that I went through in quite some detail on direct and I'm happy to go through them again with you.
Q. But all those other studies, you say, refer back to 001, correct?
A. They don't literally refer back to it. They build on it.
Q. All right. So that's what I was getting to.

If you started with the 002 study and you never had the 001 study, then you'd be in the same position with Zytiga that you were with Taxotere, right?
A. Again, this is a total hypothetical in the pretend world. If we didn't have any of these clinicals trials and any of our knowledge, then, yeah, we'd be in the same place.

But we do have it. We have the hypothesis. We have 001; we have 002; we have 003; we have 004; and we have the randomized trials times three.

Q. And the 001 study is not in the Zytiga label, correct?
A. The results are not in the clinical trials, study section or elsewhere, in the label.
Q. I'm talking about the label itself. And the -- Dr. de Bono's hypothesis is not in the Zytiga label, correct?
A. Correct.
Q. All right.

MR. KLEIN: Let's go to DDX-2701.12.

BY MR. KLEIN:
Q. And just briefly, I don't think this is disputed, but the dose of prednisone, when used with Zytiga, Jevtana and Taxotere, is all 10 milligrams a day, correct?
A. Correct.
Q. In fact, Taxotere and Zytiga both require 5 milligrams twice daily, correct?
A. Correct.
Q. All right.

MR. KLEIN: Let's go to DDX-2701.2.

BY MR. KLEIN:
Q. And this is your demonstrative with the legal standards. And I totally understand you're not a lawyer. And, for the record, it's PDX-4.3.

For direct infringement, you were instructed to assume that a person performs all steps of a claim method, right?
A. Yes.

Q. Okay. And did counsel instruct you that Janssen carries the burden of proving, for each asserted claim, that 10 milligrams a day of prednisone has anti-cancer effects, when used with abiraterone?
A. I'm sorry, repeat the question for me.
Q. Did counsel instruct you that Janssen carries the burden, for direct infringement, of proving, for each asserted patent claim, that 10 milligrams per day of prednisone has anti-cancer effects, when used with abiraterone?
A. My understanding from counsel is that the claims have defined the therapeutically effective amounts of those two drugs, abiraterone and prednisone. And, as indicated in my demonstrative, by a physician and patient performing the steps in the claim, in the same dosage, of the same drugs, in the same patients, that direct infringement will occur. That's my understanding.
Q. Okay. In your opinion, prednisone monotherapy has no anti-cancer effects, correct?
A. That is correct.
Q. And you testified that prednisone also does not have anti-cancer effects, when used with other cancer drugs like Taxotere or Jevtana, correct?
A. Those two drugs, no.
Q. And in terms of the '438 patent, you don't rely on any data in the '438 patent that shows prednisone has anti-cancer

effects when combined with abiraterone, correct?
A. Correct. There are no primary empiric data in the '438 patent.
Q. Right. And there's no hypothesis in the '438 patent that prednisone reverses resistance to abiraterone, correct?
A. Correct. But the logical conclusion from the hypothesis is embodied in the patent.
Q. You mean in the claims?
A. In the claims.
Q. Okay. There's no mention of any 001 study data in the '438 patent, correct?
A. No, but the combination of abiraterone acetate and prednisone is described in the patent.
Q. The conclusion but with no support, correct?
A. No empiric data about the 001 study in the patent, that's correct.
Q. Now, to support your opinions with regard to direct infringement, you don't rely on any studies other than the studies that Cougar or Janssen conducted in connection with Zytiga, correct?
A. So for direct infringement, I don't know that I need to rely -- and I'm not a lawyer. I'm telling you what I understand. That I need to rely on studies to establish direct infringement so long as the physician is going to directly infringe by performing the steps that are described in the

claims.
Q. And so what's your understanding of what's required to directly infringe?
A. That a person performs all of the steps of the claimed methods in the '438 patent.
Q. So that the physician prescribes 1000 milligrams of abiraterone, 10 milligrams a day of prednisone to treat patients with --
A. As therapeutically-effective amounts, yes.
Q. And what do you mean by therapeutically-effective amounts?
A. So those are the amounts that are being mentioned that are therapeutically effective to treat prostate cancer, yes. I'm in agreement with you there.
Q. So, in your opinion, if a doctor gives a patient two prescriptions, one for 1000 milligrams of abiraterone a day, second prescription of 10 milligrams per day of prednisone, because the patient is suffering from metastatic castration-resistant prostate cancer, that's all that needs to be established for direct infringement, correct?
A. That's my understanding, yes.
Q. Now, Janssen never designed a study specifically to assess whether prednisone has anti-cancer effects when used with abiraterone, right?
A. Incorrect.
Q. Prednisone?

A. I'm sorry -- you said prednisone in combination with abiraterone?
Q. Right. So let me rephrase the question.
Janssen never designed a study specifically to assess whether prednisone is having anti-cancer effects when it's used with abiraterone?
A. What I'm saying is that those studies were designed.
Q. Which studies are you referring to?
A. So 001 --
Q. Let's say -- okay -- 001, go ahead.
A. Okay. So let me be sure I'm answering the question.
Q. Okay. Let me rephrase it to make sure we're on the same page.
A. Yeah.
Q. Janssen never specifically designed a study to isolate whether prednisone is having anti-cancer effects as part of the combination of prednisone and abiraterone, correct?
A. And I'm saying that's incorrect.
Q. Okay. Because of the 001 study?
A. The 001 study and the fact that the 00 -- the 002 and 004 studies were done, further provides controlled evidence that -- or evidence that there's a real impact of the combination.
Q. Okay. Well, let's take a look at those studies.
MR. KLEIN: Let's go to DDX-2701.15, please.
BY MR. KLEIN:

Q. This is the -- do you recognize this as the Attard 2009 article, right?
A. Yes.
Q. And it's JTX-8086.1. And this is an article discussing 001 study, right?
A. Yes. What was the question?
Q. I think I just asked whether this article is discussing the 001 study.
A. It's -- yeah, it also has I guess 002 -- yes.
Q. And it's, again, it's the 001 study that you rely on most heavily to show that prednisone is having anti-cancer effects, correct?
A. I haven't done an analysis of the relative contribution of the different studies in terms of my analysis but this, I would say, certainly plays an important part.
Q. Okay. And the articles you cite that talk about reverse resistance to abiraterone are referring back to the 001 study, right?
A. The reversal -- yeah, those are the extension studies. That's what we're talking about with the reversal of resistance, yes.
Q. And on direct, you looked at a number of other articles that talk about the concept of reversed resistance of abiraterone provided by prednisone. All of those articles are footnoting or relating back to the 001 study results, right?

A. Yes.
Q. Okay. And there hasn't been any other study conducted to assess whether prednisone reverses resistance to abiraterone, right?
A. Not that I'm aware of.
Q. Okay. Now the 001 study wasn't designed to test whether prednisone is having anti-cancer effects, right?
A. No, I wouldn't quite agree with that, no.
Q. Okay.
MR. KLEIN: Well, let's go to DDX-2701.16.
BY MR. KLEIN:
Q. And I don't think there's a dispute about this, but the 001 study used a different drug; dexamethasone, right?
A. Yes. And if I can give you my answer?
Q. Well, again, that's for redirect.
A. So the protocol says dexamethasone. Yes, you're correct.
Q. All right. And let's talk about the study a little bit.
So there were 54 patients in this study?
A. Yes.
Q. All right. And none of the patients was given prednisone, right?
A. None of the patients were given prednisone.
Q. Okay. Prednisone and dexamethasone, we can agree they're different drugs?
A. They're different drugs but belong to the same class of

drugs.
Q. Right. I'll agree with that. Okay.
But they have different chemical structures, right?
A. That's true.
Q. They have different potencies?
A. That's true.
Q. So they're taken in different doses, right?
A. That's true.
Q. And in this study, dexamethasone was given in .5 milligrams per day, right?
A. Yes.
Q. The dose for CRPC, in the Zytiga label, is 20 times that, right?
A. 20 times that? I'm sorry, where did you get that number?
Q. 20 times .5.
A. But they're not -- they are not biologically equivalent.
Q. I'm just doing math. I'm not -- so your saying -- what's not biologically equivalent?
THE COURT: You're saying the dose of prednisone is 25 or the dose of dexamethasone?
MR. KLEIN: Yes.
BY MR. KLEIN:
Q. Let me put it in different way so it's not confusing.
The dose of dexamethasone, in the 001 study, is .5 milligrams per day, right?

A. Yes.
Q. And the dose of prednisone, in the Zytiga label, is 10 milligrams per day, right?
A. That's the approximately equal potent dose.
Q. Okay.
MR. KLEIN: Let's go to DDX-2701.17.
BY MR. KLEIN:
Q. We're on the same article, JTX-8706.4.
A. Okay.
Q. And you talked about this paragraph on direct, right?
A. Yes.
Q. So your testimony as to the reverse of resistance focused on the 11 of the 30 patients that had previously experienced progression on dexamethasone, group 1, right?
A. That was part of the focus.
Q. Okay. You know the two charts in Attard 2008, patient A and B?
A. Yes.
Q. Okay. Those were patients who previously experienced progression on dexamethasone, right?
A. Before they had started abiraterone, yes.
Q. So those two patients -- we don't know who they were, but those two patients were in this group 1, right?
A. Yes.
Q. Okay. And so there were 11 patients in this group?

A. Hmm-hmm -- yes.
Q. And these 11 -- only four of the 11 patients had greater than or equal to 50 percent declines in PSA, right?
A. You used the word "only." I would not agree with that term, so I would not agree with your statement.

I think it was a shocking result that was unexpected and established the hypothesis. So I would not use the word "only." So in that way, I disagree with you.

Q. Okay. I get it. Let me rephrase the question so the record is clear.

Four of the 11 patients, in group 1, had greater than or equal to 50 percent declines in PSA, correct?
A. That's correct.
Q. Okay. And so 64 percent of the patients, in group 1, did not have greater than or equal to 50 percent declines in PSA, right?
A. That's the math.
Q. Okay. Good. Only two -- only data for two of these four patients were actually charted out in the Attard articles, right, patients A and B that we looked at?
A. I believe that's correct.
Q. Okay. And so the Attard articles, when they talk about reversal of resistance, are focusing on these two of 54 patients in the entire study, right?
A. No, they're talking about the four patients who responded.

They're showing the figure of two in the Attard 2008. We're talking about 2009, correct?

Q. Okay. So they're focusing -- the reversal of resistance is focusing on four of the 54 patients, correct?

A. No. They're talking about all of the patients, both the group 1 patients who had dexamethasone previously prior to abiraterone as well as those that didn't.

The -- they both provide evidence -- they both provide evidence that there's reversal of resistance.

The higher level of evidence, perhaps, is in the group 1 patients, but they both provide evidence, to me.

Q. The articles don't have charts for data from any of the patients other than those two, right?

A. They don't have charts, but the data are presented.

Q. Well, you don't know -- you know what I'm talking about with the A and B, they're actually graphs that show dexamethasone. Abiraterone is given, the dexamethasone is added, PSA declined. Do you know what I'm talking about?

A. I do know what you're talking about, but the data for all of the patients are presented here.

Q. Okay. But the reversal of resistance hypothesis is focusing on those two patients, correct?

A. Incorrect is what I'm telling you.

If you look at the section, okay, I'm reading the same section as you are. They're including both the group 1 and

group 2 patients. They're both informative about reversal of resistance.

Q. There certainly wasn't reversal of resistance in even a majority of the patients in this study, correct?

A. That's the math, yes.

Q. Okay. And this reversal of resistance you're talking about was measured by declines in PSA over 50 percent, correct? That's the measurement?

A. That's the measurement that's used, yes.

Q. And the 001 study does not have a placebo on it, correct?

A. That's correct.

Q. And I believe, on direct, you said that the effects in the 001 study are, quote, rare times rare times rare, right?

Do you remember that?

A. That's right, I do remember that.

Q. Okay. And you said there were a relatively few number of patients, right?

A. I don't quite state that. What I said was that one achieved -- one confirmed the hypothesis with a relatively few number of patients.

Q. Okay. And before the 001 study, there were no reversal of resistance effects from any corticosteroid, correct?

A. Yes -- yes.

Q. Okay. And there were no studies done after the 001 study to confirm the effects that we saw in the study, for example,

the patient A and B, correct?
A. No, I would say that's incorrect.
I would use the additional studies that were done to further confirm that this reversal resistance phenomenon was real, further engrained it into my brain.
Q. But there were no further studies that do the same type of design where you have abiraterone, and then you add the corticosteroid later and see if there's a reversal of resistance effect in that type of matter, correct?
A. There's no need to design such a study. It was already done.
Q. Okay. And I'm not asking whether there's a need to. There just wasn't another study, correct?
A. Yeah.
Q. Okay. And so there wasn't any specific test for reversal of resistance with prednisone as opposed to dexamethasone, correct?
A. So a study that was designed in the 001 fashion was not performed specifically with prednisone, correct.
Q. Thank you. Yes.
And you don't know if the co-administration of abiraterone, in combination with dexamethasone, would compare equally with the combination of abiraterone and prednisone, right?
A. Wrong.

Q. You have no clinical evidence to assess whether the co-administration of abiraterone, in combination with dexamethasone, is as effective in treating prostate cancer as the combination of abiraterone and prednisone, correct?
A. Not quite. So no prospective randomized controlled trial has been done comparing the two, but that would not be -- not be required because we know that prednisone and dexamethasone can both achieve the effect of -- in combination with abiraterone acetate.
Q. You've seen no clinical evidence -- not necessarily randomized phase III trials, but no clinical evidence that the co-administration of abiraterone acetate, in combination with dexamethasone, is as effective in treating prostate cancer as the combination of abiraterone acetate and prednisone, right?
A. Yeah. I think -- let me just answer your question as best as possible. Because you're using the word "clinical evidence," and I think you're trying to apply it to specific studies that compared the results of abi -- abiraterone prednisone to abiraterone dexamethasone, but that's not the limit of the world of clinical evidence.

The world of clinical evidence also includes our understanding of how the two work together and how both drugs, dexamethasone and abiraterone, have been shown -- can -- to suppress ACTH drive in the upstream steroids.
Q. So are you disagreeing with my question?

A. I'm trying to answer it carefully because you're using the word "clinical evidence" in a way that needs to be more specific for me to give you a yes or no answer.
Q. Okay.
MR. KLEIN: Well, let's put on the screen Exhibit 1189, which is your IPR deposition, Page 11, Lines 11 through 19.
BY MR. KLEIN:
Q. And so you said I was using the term "clinical evidence."
This is a deposition from the IPR, and the question was: "But as of today, in 2016, is it your opinion that the co-administration of abiraterone acetate, in combination with dexamethasone, is as effective in treating prostate cancer as the combination of abiraterone acetate and prednisone?
"ANSWER: I have no information in that regard, no clinical evidence in that regard, nothing that I could point to."
Is that your testimony?
A. I would like to see my entire deposition before I answer that question.
Q. Your counsel can ask you additional questions on redirect. My question is simply, was that your testimony?
A. That's what it states.
MR. KLEIN: Let's go to DDX-2701.18.
BY MR. KLEIN:

Q. Okay. Here we go. On the screen is DTX-1190.1.

Do you recognize this as the Ryan 2011 reference?

A. Yes.

Q. Okay. And this article relates to the 002 trial, right?

A. Yes.

Q. Okay. And this was a phase II trial, right?

A. Correct.

Q. And it had 33 patients?

A. Correct.

Q. And unlike the 001 study, this study did use prednisone, right?

A. Correct.

Q. Okay. But you see there's the purpose, the paragraph "Purpose"?

A. Hmm-hmm -- yes.

Q. Okay. The stated purpose focused on abiraterone's efficacy, right?

A. Wrong.

Q. Okay. The term "prednisone" isn't even in the purpose paragraph, right?

A. It's not in the purpose paragraph, but it's throughout the entire manuscript.

Q. Okay. Can we agree that the purpose of the study was not to assess whether abiraterone -- I'm sorry, let me rephrase.

The purpose of the study was not to assess whether

prednisone is actually achieving anti-cancer effects independent of any effects abiraterone is having, correct?

A. If this study were hypothetically done in the context of no other knowledge about abiraterone or prednisone, we pretend we're reading this and have no other knowledge, no scientific knowledge. There's no -- all they're looking at is the combination of abiraterone acetate and prednisone.

But again, I think I analogized this to your label line of questioning. It's not realistic to do that.

Q. Okay. Fair enough. But what I was getting at is the 001 study had already happened, right?

A. That's -- I don't know the date of the conclusion of the 001 study and the initiation of this one, so maybe you can enlighten me on those dates.

Q. Okay. Well, my point is, the purpose of the study -- putting aside what a skilled artisan would know, the purpose of conducting the 002 study was not to see if prednisone is independently having anti-cancer effects distinguished from abiraterone anti-cancer effects. That's not the purpose of the study, right?

A. The purpose of the study was to test the effects of the combination.

Q. Right. That's what I was getting at. Okay.

And there was no placebo arm in the 002 study either, right?

A. No placebo arm.
Q. And there's no comparison of abiraterone's anti-cancer effects to the effects of the combination, correct?
A. No. I just -- I -- earlier, on direct, I gave you a comparison of abiraterone to abiraterone and prednisone.
Q. I'm sorry, in the 002 study there's no compare -- you're talking about your cross comparisons?
A. Right.
Q. Okay. In the 002 study itself, there's no comparison of effects of the combination to effect of abiraterone alone, correct?
A. Right. We talked -- this is a single-armed study of abiraterone acetate and prednisone, in combination.
Q. And there's no data from the 002 study in the Zytiga label, right?
A. Right. We touched upon that before, yes, that's correct.
Q. Okay. We talked about the 001 study. And just to be clear, there's no data from either the 001 study or the 002 study in defendants' proposed generic product labels, right?
A. Yes, there's no information that's specifically called out about the data from those studies in those labels.
Q. And there's no data from the 002 study in the '438 patent either, right?
A. Yes. We touched upon that earlier.
Q. Okay.

MR. KLEIN: Let's go to DDX-2701 --

THE COURT: When you get to a convenient break point -- I don't want to cut you off in the middle of a point, but when there's a convenient break.

MR. KLEIN: I don't have that much longer, so --

THE COURT: Maybe we should press on then. Okay.

MR. KLEIN: All right.

Let's go to DDX-2719.19.

BY MR. KLEIN:

Q. Dr. Rettig, you recognize this as PDX-4.63 from your direct?

A. Yes.

Q. Okay. And is this is the cross-comparison that you were just referring to a moment ago, right?

A. Yes.

Q. Okay. And what you did here was you compared the results of part of the 001 study to the 002 study, right?

A. Yes.

Q. Okay. And generally speaking, cross-study comparisons are disfavored, correct?

A. Incorrect.

Q. Okay. So, in your opinion, from a scientific perspective, a cross-study comparison would constitute an adequate and well-controlled study design?

A. Yes. So let me give you an example. So the way I would

describe this is what we call a case control study of this cross-comparison. We have two endpoints. Look back in time at the patients. Similar patients, yes, we get an answer.

One of the most important health policy decisions ever in human history was based on a case control study, and that was tobacco, smoking. What we did was took smokers, people who died from lung cancer and those that didn't, who developed lung cancer and those that didn't. We looked back and asked, Is there a difference in smoking rights. So I think it's a very valid comparison.

Q. In your view, would you characterize cross-comparison studies like what you did in PDX 4.63 as the epitome of clinical science, to borrow a phrase you used on direct?

A. In isolation, I would not. What I was referring to, in direct, was the whole process from hypothesis to phase I, phase II, phase III combination. That's what I was talking about --

Q. Yeah, and I'm --

A. -- an epitome.

Q. Right. And I was just asking you about this study. I understood your testimony from direct, but you wouldn't characterize a cross-comparison study as the epitome of clinical science just in general. Ideally, you want to have a single study, correct?

A. The highest -- I would agree, the highest level is a randomized controlled trial -- prospective randomized

controlled trial.
Q. And neither -- we covered this. Neither of the two studies that you're comparing had a placebo arm, right?
A. No. Yes, you're correct.
Q. Okay. And what you did here is you compared time to PSA progression from the 001 study to the 002 study?
A. Essentially.
Q. Yeah. And the 001 study had a 7.5-month time to PSA progression, right?
A. Yes.
Q. And the 002 study had a 16.3-month time to PSA progression?
A. Yes.
Q. Okay. So are you testifying that this cross-comparison chart proves that prednisone more than doubles the anti-cancer effects of abiraterone?
A. That's what it seems to me. Let me give you some understanding then. If we give prednisone by itself, if it were not cooperating, we would expect a median time to PSA progression of two to three months, and now we're seeing one that's about nine months. Okay?
So given the 001 study and looking at this, I think the hypothesis has been established.
Q. But you're not saying, looking at the cross-comparison study, that prednisone doubles the anti-cancer effect of

abiraterone? You can't say that just from this cross-comparison, right?

A. I can't tell you quantitatively the role of prednisone -- the effect of prednisone on the overall effect of the combination from looking at these two studies.

Q. Okay. And there's obviously no cross-comparison data for the 001 study and the 002 study --

THE COURT: Excuse me. If you just back up one second.

MR. KLEIN: Yeah.

THE COURT: Is the reason for your last answer the confidence interval? Because I guess what I'm talking about before that is, you know, arithmetic says, you know, 16 is about twice 7.5, but is it because of the confidence intervals of the two?

THE WITNESS: So I was responding to a potential criticism that had come out by the defendants that had been reported that the confidence intervals can overlap.

As you remember, the upper end of the confidence interval just barely -- and what I was saying in my testimony was that's really, really very modest, and I can still make an interpretation based on the cross-study comparison, despite this -- the extremes -- the overlap in the extremes of the confidence intervals.

THE COURT: Right. But what I'm getting at is, what

is the reason that you're saying, look, I can't quantify it in that way, I can't say the two is doubled?

THE WITNESS: I see. So when -- studies that require assessments of drug interactions are very challenging. I'll give you an example. So if one were to try to take drug A and drug B, in order to establish the drug interaction, let's say, even in a petri dish, one would take two concentrations at -- a concentration of each drug had a fixed ratio and then use it at ever increasing doses and assess the impact of the combination -- whatever, on a prostate cancer cell life -- and then one uses the data and calculates something called a combination index.

So that's how something is done in a petri dish. So you can imagine that something like that, in a human being, is not feasible. It's not very easy to do in an animal, in a small animal.

THE COURT: That's all.

MR. KLEIN: Okay.

BY MR. KLEIN:

Q. PDX 4.63 doesn't contain a statistical analysis, right?

A. Correct.

Q. And there's no cross-comparison of the 001 and 002 studies in defendants' generic abiraterone product labels, correct?

A. Correct.

MR. KLEIN: Let's go to DDX-2701.20.

BY MR. KLEIN:

Q. And all I've done here is put, you know, summaries of the 301 and 302 studies on the screen. This is from DTX-1580.22 and .24.

You're obviously familiar with these studies, right?

A. Yes.

Q. These are phase III studies?

A. Yes.

Q. And these are the studies that are in the defendants' labels, right?

A. Yes.

Q. And the active arm in both trials was 1000 milligrams of abiraterone and 10 milligrams of prednisone, right?

A. Yes.

Q. Per day.

A. Per day.

Q. And the placebo arms of both trials, also, contain 10 milligrams per day of prednisone?

A. Yes.

Q. Okay. And so the 10 milligrams per day of prednisone was obviously in both the treatment and placebo arms?

A. Yes.

Q. And so it's clear that these two studies weren't specifically designed to distinguish the effects of prednisone from a placebo, right?

A. Yes, these studies were not designed to establish the specific quantitative role of prednisone in the overall effect with abiraterone acetate with Zytiga.

Q. And neither the 301 or 302 study was designed to distinguish the effects of prednisone from the effects of abiraterone alone, correct?

A. They were designed only to assess the effects in combination, and they were -- but when they were designed, they were designed based upon other studies.

So there's no reason, there's no motivation to do such a study. I talked about that -- I talked about that on direct.

Q. I understand. I'm not asking questions about motivation, I'm just asking you about how these two particular studies were designed.

Do you agree that neither the 301 nor the 302 study was designed to distinguish the effects of prednisone from the effects from abiraterone alone?

A. Effects of prednisone and abiraterone alone? Can you please restate the question? I'm sorry.

Q. Yes. Neither the 301 nor the 302 study was designed to distinguish any anti-cancer effects from prednisone from anti-cancer effects of abiraterone when taken alone?

A. When taken together -- when taken -- what was the last part?

Q. Let me rephrase the question.

Neither the 301 nor the 302 study was designed to assess and compare the effects of the combination to the effects of abiraterone alone?

A. Right.

Q. Okay. And you're not aware if anyone has ever designed a study designed to determine the relative quantitative contributions of each of abiraterone and prednisone to the overall survival efficacy you get with the combination, correct?

A. Correct. No such study would ever be done, I would imagine.

MR. KLEIN: Okay. No further questions.

THE COURT: Okay. Let's now take our break. It's 3:50. Let us come back at 5 past 4.

(Recess at 3:51 p.m. to 4:07 p.m.)

THE COURT: Are you ready?

MR. KRAUSE: Yes, Your Honor.

THE COURT: Let's resume.

REDIRECT EXAMINATION

BY MR. KRAUSE:

Q. Dr. Rettig, do you recall that you were asked, on cross, about DTX 1697?

A. I believe so, yes.

Q. If you could find it in your binder.

THE COURT: I'm sorry, we're in your binder now?

MR. KRAUSE: I'm sorry, defendants' binder.

THE WITNESS: Yes, I got it.

BY MR. KRAUSE:

Q. And I believe you were indicating that you believe that these slides reflect the fact that prednisone and abiraterone acetate, in combination, have an anti-cancer effect. Is that right?

A. Yes.

Q. If you could turn to the page DTX 1697, Page 13.

What does this -- I'm sorry --

A. Got it.

Q. What does this page reflect with respect to your views and what you would be imparting to an audience?

A. So this is sort of the -- what I'll call the money slide, if you will. It's towards the front of the slide deck and it is showing the survival advantage of the combination of abiraterone acetate plus prednisone over the control arm of the 302 study.

Q. Did you ever suggest to an audience, in your talks, that abiraterone acetate and prednisone's efficacy might be due to abiraterone acetate alone?

A. Never.

Q. If you could also turn to Page 16. This is, again, is DTX 1697.

A. Okay.

Q. And again, what information is this relaying with respect to your talks?
A. So this is the 302 study looking at a cold primary endpoint. So not overall survival, but radiographic progression-free survival. Also showing the marked improvement in radiographic progression-free survival. You can see the numbers there. They are strikingly different.
Q. So does this graph, in this information relate to side effects?
A. No.
Q. What does it relate to?
A. Efficacy. Anti-cancer effect.
Q. If I could ask you to turn, in your binder, to JTX-8086, please.
A. Okay.
Q. You were asked about whether this study -- this is Attard 2009; is that correct?
A. Yes.
Q. Whether it was designed to assess the contribution of prednisone to the combination of abiraterone acetate and prednisone, and counsel focused you on dexamethasone.

I think you were cut off in your explanation of the relationship between dexamethasone and prednisone with respect to the activity. Would you like to express your views?
A. Yes, thank you.

I was trying to express that, for the purposes of interactions with abiraterone acetate, prednisone and dexamethasone are interchangeable. It's a class effect. They'll both suppress the concentrations of upstream steroids that occur as a result of the CYP17 blockade by abiraterone acetate.

Q. I believe counsel also said something to the effect that the only figures reflecting a benefit to patients was in figure A.1 of the Attard 2008 paper. I would like to direct your attention to the final page JTX-8086, the same document.

A. Okay.

Q. Oh, I'm sorry, the second to the last page.

A. I see it. Yes.

Q. And, Doctor, what does this reflect?

A. So this is another graphical representation of how the PSA changed in all of the patients who were in the extension study. So in red are group 1, in blue is group 2.

If you remember, group 1 had the dexamethasone prior to abiraterone, before it was then added back. And group 2 was the group that had not received dexamethasone prior to its being added back. And each column represents an individual patient.

And you can see the zero here -- I'll circle it for you -- and that represents the patient's own baseline value.

So when it goes down, that's indicating that the

patient had a PSA fall. And you can see the magnitude of the drop in percentage for each patient and the magnitude of the increase. And this is also called the waterfall plot, it looks like -- I don't know -- a waterfall.

Q. What does this tell you about the activity of dexamethasone or glucocorticoid?

A. That it's very active and surprisingly so. In combination with abiraterone acetate.

Q. If we could turn now to DTX-1190.

A. Got it.

Q. And I believe you were asked a number of questions emphasizing the part of the abstract entitled "purpose" and the fact that abiraterone -- that word alone is provided there, suggesting that somehow prednisone was not also in combination.

What's your understanding of the results of this paper?

A. This -- the results are about the combination of abiraterone acetate and prednisone and the -- its impact on various clinical measures of response.

And my interpretation, especially in light of the abiraterone acetate monotherapy results, was that this study, with the combination of abiraterone acetate plus prednisone, yielded a clinically meaningful improvement in those results.

Q. And what does the title of this paper tell you about whether its stating abiraterone acetate alone or abiraterone

acetate in combination of prednisone?
A. Well, that's right there in the first line of the title, phase II study of abiraterone acetate plus prednisone.
Q. If you could turn to PDX-4.63.
A. Okay.
Q. You were asked questions about this as well; is that right?
A. Yes.
Q. Is there any explanation for the difference in time to PSA progression, between Attard 2009 and Ryan 2011, other than prednisone was contributing an anti-cancer effect with abiraterone acetate?
A. Not in my analysis.
MR. KRAUSE: No further questions.
THE COURT: Okay. Not much there, but any redirect -- or recross, excuse me.
MR. KLEIN: No, no recross.
THE COURT: You may step down, sir.
(Witness excused.)
THE COURT: Okay. Let's just talk scheduling. Is there anything we can productively do with the limited time left today?
MR. REIN: Your Honor, that is our last witness in our case in chief, which I've provided, as I indicated on the phone -- I guess it was last week now. One of our witnesses,

Mr. Vellturo, is on trial right now. He is primarily a validity witness, but he's going to have some testimony on the infringement issue.

On top of that, we have a biostatistician who's providing testimony in the rebuttal portion of our case relative to the infringement case. But with that, we would pass the case over to the defendants.

THE COURT: Okay. Once again, let me ask whoever would like to speak, is there anything we can sensibly do in the time remaining or should we do a little business, call it a day and start in the morning?

MS. BLOODWORTH: Your Honor, we have a couple of depositions that we could play. One is 20 minutes and one is 27 minutes, if you wanted to fill the time.

THE COURT: Maybe we could just do one dep excerpt and take it from there. On the subject of scheduling, though, is it tomorrow --

I just wanted to tell all counsel tomorrow I have a criminal matter at 12:00. What that means is we'll take a long lunch break, long mid-day break, probably from 12:00 to 1:45 should do it. So just so your aware of that. Okay.

MS. BLOODWORTH: Can I ask you about Friday, Your Honor?

THE COURT: Yeah. And on Friday I have a matter in the afternoon -- I have a matter beginning at 2:00. By the

time that's over, I think it would be pointless for us to start-up again. So why don't we call it a day before that 2 o'clock matter. Maybe, you know, 1:15 or so.

MS. BLOODWORTH: I think, Your Honor, my understanding is plaintiffs need to call their -- Dr. Ballman this week. And I know Dr. Mega, our oncologist, can only go on Friday. So with that said, I think we would like to start Dr. Nagaich now and get his --

THE COURT: Sure.

MS. BLOODWORTH: -- the 45 minutes in so that we can keep the schedule of live witnesses moving.

THE COURT: Okay. We can do that. And, of course, it being a bench trial, we can call witnesses out of order, if we really need to. It's not a big deal. If we can accommodate people.

MS. BLOODWORTH: We'll refigure our seats here.

THE COURT: Sure.

MS. BLOODWORTH: Thank you, Your Honor.

AKHILESH NAGAICH, DEFENSE WITNESS,

having been duly sworn, testifies as follows:

THE COURT: Okay. When you're ready.

DIRECT EXAMINATION

BY MR. WONG:

Q. Hello, Doctor. Can you please state your name for the record?

A. Akhilesh Nagaich. The spelling is A-K-H-I-L-E-S-H, last name, N-A-G-A-I-C-H.

THE COURT: And we have a new court reporter. Mr. Wong, introduce yourself as well.

MR. WONG: Sorry. Jovial Wong from Winston and Strawn.

BY MR. WONG:

Q. Dr. Nagaich, have you been asked to provide expert opinions in this case by defendants?

A. Yes.

Q. And specifically, from what perspective or expertise, are you offering your opinions?

A. I'm offering my opinion as an FDA industry expert.

Q. And have you ever testified as an expert in a court of law before?

A. No.

Q. Did you prepare some slides to help you explain your opinions to the Court?

A. Yes, I have.

MR. WONG: Let's go to DDX-22100.2.

BY MR. WONG:

Q. In general, Doctor, what do your opinions relate to?

A. My opinions relate to the infringement of the '438 patent.

Q. Okay. And what are your opinions as to the alleged infringement?

A. My opinions are summarized in the slide. I say the defendants do not induce infringement of the asserted claims of the '438 patent. And defendants do not contribute to the infringement of the asserted claims of the '438 patent.
Q. Thank you. And in a nutshell can you explain to the Court the primary reason supporting your opinions of no infringement?
A. My opinion is that FDA has not approved the use of prednisone as an anti-cancer drug, either alone or when used with Zytiga.
Q. Let's talk a little bit --
THE COURT: Let's just back up one moment. Am I correct there's no objection to the qualification of Dr. Nagaich as an expert in this area?
MR. REIN: I'm not sure what he's being proffered for, but I have no objection to his testifying as an expert on the FDA matter.
MR. WONG: I'm going to go through a little bit of background so the Court understands his background.
BY MR. WONG:
Q. Let's talk a little bit about your background, training, and work experience.
Doctor, where are you currently employed?
A. I'm employed with Emergent Biosolutions and also with the FDA Group, LLC.
Q. What is Emergent Biosolutions?

A. Emergent Biosolutions is a pharmaceutical company located in Gettysburg, Maryland. Emergent manufactures vaccines and medical countermeasure drugs.
Q. And what is your title at Emergent Biosolutions?
A. I'm a senior manager of regulatory affairs.
Q. And as a senior manager of regulatory affairs, what do you do?
A. I'm regulatory lead for a number of vaccine candidates for Emergent. I develop regulatory strategies for vaccine candidates and countermeasure drugs. I write briefing packages to be submitted to the FDA, negotiate with FDA regarding drug approvals.
Q. Okay. Doctor, in your day-to-day job activity at Emergent are you required to deal with and keep abreast of FDA regulations with respect to drug approval?
A. Yes. I am required to keep myself abreast with regulations, current regulations, as well as any changes in FDA regulations that could impact Emergent's products.
Q. And you also mention FDA Group. What is FDA Group?
A. It's an quality and regulatory consulting firm located in Westborough, Massachusetts.
Q. And what do you do at FDA Group?
A. I'm a senior quality and regulatory consultant with them. I develop, again, regulatory strategies for drugs. Mostly clients of pharmaceutical companies. I advise them regarding

FDA approval, help them write briefing packages for FDA submissions.

Q. And can you just briefly describe your educational background?

A. Yes, sure. I have undergraduate degrees from India. I am a Bachelor of Science in chemistry and biology and Master of Science degrees in chemistry. I also obtained my Ph.D. in chemistry from University of Allahabad, India.

Q. Okay. After you got your Ph.D. did you complete any postdoctoral training?

A. Yes, I had a number of postdoctoral appointments. I was a postdoctoral fellow at the molecular biophysics unit in the India Institute of Science.

I then came to U.S. and I was a postdoctoral fellow at the University of Nevada, Reno, from '94 to '99.

Then I came to NIH the National Cancer Institute, where I was an cancer training of arts fellow, from 2000 to 2005.

Q. And when you were at NCI, what kind of research did you do?

A. I worked on studying the molecular mechanisms involved in hormone action. Especially the role of hormones in oncogenesis.

Q. What does that mean?

A. That means I was looking at how steroid nuclear receptors

regulate expression in the context of chromatin, particularly in cancer cells.

Q. Okay. And you were there until 2005. Is that right?

A. Yes.

Q. Then what did you do?

A. I moved to FDA to start my own research lab.

I was a principal investigator at the Office of Biotechnology Products, and also quality and labelling reviewer for FDA submissions.

Q. And how long were you at FDA in that capacity?

A. I was there for about eight years, starting from 2005 to end of 2013.

Q. And you mentioned that you were a principal investigator. What did you do in that role at FDA?

A. I led and directed a group involved in scientific research and mentored postdoctoral fellows and other research and regulatory staff and, you know, wrote grants, published papers.

Q. Okay. And you also mentioned you had a role as a drug quality reviewer. What does that entail?

A. I was -- I was a regulatory reviewer for a number of FDA submissions, including investigation of New Drug Applications, biologics license applications, BLA, NDA, New Drug Applications, and reviewed New Drug Applications for drugs being doubled up for cancer and metabolic disorders, yes.

Q. Okay. And what qualifications do you have to have to

become a reviewer at FDA of those dossiers?
A. You have to have a solid education and training in sciences. Also you have to have some on-site training, how to perform regulatory review work and develop an insight, sort of a regulatory insight into reviewing applications.
Q. Okay. So can you explain to the Court what you did when would review a dossier or a submission by an applicant?
A. Sure. So I would review, sometimes, thousands of pages of scientific data, and then summarize that data and recommend -- recommend approvals.
Q. Okay. And was there differences in reviewers? Is there a difference between a primary reviewer and a secondary reviewer?
A. Yes. So the primary reviewer, you take a first look at the submission, analyze all the data, review all the data, all the sections of the FDA submissions, and then, you know, write -- write a summary report and your recommendation; and then as a secondary reviewer, you review the summaries of other reviewers in your group.
Q. Okay. And would you review the entire application, if it was submitted?
A. Yes, I would review the entire submission and entire application.
Q. Okay. And as a primary reviewer, did you review clinical trial data and other efficacy submissions that supported approval of an indication?

A. Yes. For investigation of New Drug Applications, I would review the entire submission. That would include chemistry, manufacturing and control, nonclinical studies as well as the proposed clinical protocols, investigator's broad shield and clinical protocols.

For NDAs and BLAs, again, I would review the entire submission. That would include CMC, labelling, nonclinical studies and pivotal clinical trial studies.

Q. Okay. And we heard a little bit about a cross-disciplinary review team. Were you part of any cross-disciplinary review teams --

A. Yes.

Q. -- while you were at FDA?

A. Yes, I was.

Q. And what is that?

A. Typically, once you -- once your drug gets some kind of an accelerated -- put on an accelerated approval pathway, FDA assembles the reviewers to really accelerate the approval pathway. And so the cross-disciplinary team is a team of about 10 to 12 FDA regulators and subject matter experts who would review and coordinate the review with different divisions.

Q. Okay. And as part of this cross-disciplinary review team, did you have ultimate sign-off authority to recommend approval?

A. Yes, I did.

Q. During your time at FDA, how many different kinds of drug

applications did you review?
A. I reviewed pre-INDs, INDs.
Q. About how many pre-INDs did you review?
A. About -- I was -- I had about 30 INDs in my portfolio, so I was responsible for the life cycle management of about 30 INDs. I may have reviewed close to 100 pre-IND applications during my tenure at FDA, about six NDAs and about two volatile license applications.
Q. Okay. And during your time at FDA, did you participate in any fellowship programs?
A. Yes. I was a preceptor for the FDA commissioner's fellowship program, and I was also a preceptor for intra-agency oncology task force, fellowship program that was a program set up by the National Cancer Institute and FDA to train the reviewers in the FDA submission work, FDA review work.
Q. Okay. During your time at FDA, were you ever involved in preparing FDA guidances?
A. Yes, I was. I was part of the working group to draft regulatory guidances for -- for bio-similar drugs.
Q. And what would you help draft in that regard?
A. My primary focus was on quality and labelling aspect of the guidance documents.
Q. Okay. You said you were at FDA until 2013. What did you do then?
A. I moved back to NIH for a couple of years, and then

subsequently moved to USP.

Q. What is USP?

A. USP is called United States Pharmacopeia, which is a nonprofit organization, roughly about 200 years old, and USP sets the standards for drugs, biologics and dietary supplements in the United States.

USP is also directly into Food, Drug, and Cosmetics Act, and so USP standards are enforced by the FDA. USP general chapters, there are below 1,000, are enforced by the FDA.

Q. And what were you doing at USP?

A. My role was, I was assigned for an expert committee on labelling and nomenclature of drugs and biologics. I was involved in drafting and revising a chapter on drug labelling. So I was liaisoning with an expert committee of about 12 experts from industry, FDA, academia and other regulatory bodies across the world, including WHO.

Q. Okay. And after USP, did you go to Emergent Solutions where you are now?

A. Yes.

Q. Thank you.

MR. WONG: Your Honor, defendants tender Dr. Akhilesh Nagaich as an expert in the field of drug regulations, drug labelling, drug approval and FDA.

MR. REIN: No objection.

THE COURT: Okay. Dr. Nagaich is obviously well

qualified by his background and training to give opinion testimony in those areas, and I'll accept his testimony as such. Continue.

MR. WONG: Thank you.

BY MR. WONG:

Q. Dr. Nagaich, with respect to your opinions on alleged infringements, did you prepare a slide that reviews the legal standards that you applied and as you understand them?

A. Yes, I did.

MR. WONG: Let's go to the next slide, DDX-2100.4.

BY MR. WONG:

Q. Doctor, what is your understanding as to induced infringement?

A. My understanding of induced infringement is that there would be no induced infringement if the claimed use of the '438 patent is not FDA approved.

Q. Okay. So let me ask you this: Is the method of treating prostate cancer that is claimed in the '438 patent approved by FDA?

A. No.

Q. And what is your understanding as to the requirements for contributory infringement?

A. My understanding is that there will be no contributory infringement if the FDA approved use is a substantial non-infringing use, or the claimed use of the '438 patent is an

off-label use.
Q. Okay. So is the FDA-approved indication for treating mCRPC that is found in the Zytiga label, as well as in defendants' proposed labelings, a substantial non-infringing use?
A. Yes, it is.
Q. All right. Let's move on to the asserted claims.
Doctor, have you reviewed the claims of the '438 patent?
A. Yes, I have.
MR. WONG: Let's go to the next side, DDX-2100.5.
BY MR. WONG:
Q. Is this claim 1 of the '438 patent?
A. Yes. The top slide, that is claim 1 of the '438 patent.
Q. And generally, what is your understanding of claim 1?
A. Well, it's a method of use patent. And the claim 1 states that a method for the treatment of prostate cancer in a human comprising administering a therapeutically effective amount of abiraterone acetate and a therapeutically effective amount of prednisone.
Q. Doctor, have you also reviewed the Court's claim construction order with respect to the terms "treatment" and "treating"?
A. Yes, I have.
Q. And what is your understanding of the Court's order?

A. My understanding is that treatment or treating means the eradication, removal, modification, management or control of a tumor or primary, regional or metastatic cancer cells or tissue and the minimization or the delay of the spread of cancer.
Q. Do you have a shorthand understanding as to what that means?
A. That means that both prednisone and abiraterone acetate must contribute in the eradication -- as an anti-cancer drug.
Q. Thank you. And did you apply this claim construction to your analysis of whether or not defendants infringed the claims of the '438 patent?
A. Yes, I have.
Q. Now, if independent claim 1 is not infringed, what is your opinion as to whether defendants infringe any of the other asserted dependent claims, 4, 8, 11, 19 and 20, of the '438 patent?
A. My understanding is that if the independent claim is not infringed, then the dependent claims are also not infringed.
Q. All right. So for the record, have you been in the courtroom since opening statements on Monday?
A. Yes, I have.
Q. Okay. And were you in the courtroom when Ms. O'Shea described the FDA approval process?
A. Yes, I was.
Q. What did you think of her explanation?

A. In general, I agree with her explanations. I would have explained things slightly differently, though.
Q. Doctor, do you have slides that describe the process for the FDA to approve a drug?
A. Yes, I do.
MR. WONG: Let's go to the next slide, DDX-2100.6.
BY MR. WONG:
Q. What is shown here, Doctor?
A. Broadly speaking, the FDA approval process comprises the four major steps. You have a preclinical research, followed by clinical research, then FDA review, and then FDA post market safety monitoring.
Q. Okay. Let's look at the first step. The preclinical research step, what's entailed in this first step?
A. The preclinical research is a stage where a lot of animal studies are carried out to study toxicity of the drug in animals. FDA would not allow administration of the drug in humans unless a safety has been established in animal models.
Q. Okay. What happens in the next step, clinical research?
A. Once the safety data is gathered in animal models, sponsors, they seek out a pre-IND meeting with the agency to discuss their proposed clinical development plan, and then they submit something called IND, Investigational New Drug Application.
The FDA reviews the IND, and then if they are

satisfied that -- satisfied that there are no potential safety concerns with their proposed protocol in the drug, they allow INDs approved and the sponsors, they can proceed with the phase I trial.

Q. Okay. And what is a phase I trial?

A. A phase I trial is a small trial, roughly about 20 to 80 subjects, and the primary goal is to gather safety data regarding a drug, typically like the first inhuman study to gather safety and sometimes gather activity information of a drug.

Q. Do phase I trials ever measure the efficacy of a drug?

A. They are not required to make an application, but for certain therapies, preliminary efficacy data are derived from -- from the phase I studies as well.

Q. Is it particularly common in one therapeutic area?

A. Yes, particularly in oncology -- oncology indications.

Q. What happens after the phase I studies are completed?

A. The sponsors will typically have an end of phase I meeting with the FDA, submit their phase I studies, and then in that meeting, they try to discuss their proposed study plan for the phase II stage.

Q. Okay. And can you describe what a phase II study is, then?

A. Phase II studies are slightly larger studies. And it's the primary goal of the phase II study, to gather efficacy data

regarding the drug and also look for short-term risks associated with the drug.

Q. And what happens after phase II studies are completed?

A. Again, I think the sponsors, they would like to have an end of phase II meeting with the FDA to discuss their pivotal plan for their pivotal clinical trials.

Q. And would those be the phase III trials?

A. Yes.

Q. Okay. What happens or what is a phase III study?

A. The phase III studies are pivotal clinical studies that would support labelling claims. And the primary goal of these studies is to look at the risk and benefit, gather more data regarding efficacy, and then also assess the risk/benefit ratio or risk/benefit assessment of the drug.

Q. Doctor, do the FDA regulations describe what is required for FDA approval of a drug in terms of clinical trials?

A. Yes.

MR. WONG: Let's go to the next slide, DDX-2100.10.

BY MR. WONG:

Q. What is shown here, Doctor?

A. This slide shows the clinical trial requirements to support an approved indication. And this is an excerpt from 21 CRF Part 201.57(c)(2)(4), and it states that for drug products other than biological products, all indications listed in this section must be supported by substantial evidence of

effectiveness based on adequate and well-controlled studies as defined in Part 314.126(b).

Q. Okay. And we'll look at that part, but when it says, substantial evidence of effectiveness, what's required there? I mean, why does it require such a high degree of evidence?

A. The FDA will not approve a drug unless there is a substantial evidence for its effectiveness.

Q. Let's look at the next slide.

Doctor, what is shown here on this next slide? For the record, it's DDX-201.11.

A. So this an excerpt from 21 CFR 314.126(b)(2), and this describes the statistics of an adequate and well-controlled study. And it states the study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.

Q. And why is that required?

A. You need to have a proper control to quantify a drug, a drug effect.

Q. Okay. And how would you design a study to be adequate and well controlled?

A. So, typically, in a control experiment, you change one variable at a time. And then in a trial, you have a control arm and you have an experimental arm or an active arm. And a control arm receives everything other than the active component or active drug that you are trying to test.

Q. All right. Let's go back to the approval process. What is the next step after the clinical research step?
A. So after the phase III trials are completed, sponsors, they write an NDA, New Drug Application, and then submit all their studies to FDA.
Q. And to be clear, during your time at FDA, did you actually review and recommend for approval NDA submissions?
A. Yes, I did.
Q. If an NDA is approved by the FDA, what happens next?
A. Once the NDA is approved the FDA issues an approval letter. Sponsors are allowed to market the drug, introduce the drug into interstate commerce.
Q. How will FDA communicate an approval to the applicant?
A. FDA sends out an approval letter.
Q. Will FDA, also, make available to the public the basis and rationale for that approval?
A. Yes. At some point after the approval, FDA puts together this approval package and then -- describing the reviews from different reviewers and then make them available on their website.
Q. Okay. Let's go to the last step in the process. What is FDA post-market safety monitoring?
A. So after the drug is approved, the post-safety -- post-market safety monitoring continues. There's a database where adverse events associated with the drug are reported with the

drug -- adverse events are reported.

Also, if a sponsor wants to expand their label or change the manufacturing side or -- and make any change in the process, they are -- what they do is they submit a supplemental application called SNDA or supplemental NDA to the FDA.

Q. All right. Thank you.

Let's start talking about your substantive opinions as they relate to the alleged infringement. Doctor, can you remind the Court again why you think the defendants do not induce or contribute to infringement of the '438 patent?

A. Because I think the FDA has not approved prednisone as an anti-cancer drug.

Q. Okay.

A. Either alone or in combination vis-à-vis.

Q. Doctor, let's start with monotherapy prednisone. Has FDA ever approved prednisone as a monotherapy as an anti-cancer treatment?

A. No, it has not.

Q. How did you come to that opinion?

A. I reviewed all the available package inserts for prednisone, and I have not seen any indications as an anti-cancer for prednisone.

Q. Okay. And in reviewing those prednisone labels, what indications did you see that FDA approved and that are relevant to our case here?

A. I believe I have a slide on this. But prednisone is sort of a classic antiinflammatory drug. I have seen that it has been approved as a glucocorticoid replacement. It has been approved for palliative use, and for endocrine disorders.

Q. Let's take a look at an example.

MR. WONG: Can we see JTX-8125.

BY MR. WONG:

Q. Doctor, what's on the screen here, what is this document?

A. This is a package insert of one of the prednisone drugs that is available in the market called prednisone tablets USP.

Q. Okay. And let's go to Pages 2 and 3 of this document.

MR. WONG: Can we, also, have Page 3 up.

BY MR. WONG:

Q. Great. What is listed here on Pages 2 and 3, generally?

A. So in Page 2 and 3, indications and usage of prednisone are listed.

Q. Okay.

A. As you can see, there are a number of indications.

Q. Let's look at the first indication, I believe it says "endocrine disorders." What does it describe here in prednisone's first indication?

A. It says that it's approved for endocrine disorders, primary or secondary adrenal cortical insufficiency, hydrocortisone or cortisone is the first choice.

Synthetic analogs may be used, in conjunction with

mineralocorticoids with Eplerenone -- basically, it is approved for primary or secondary adrenal corticoid insufficiency.

Q. Okay. And I think you also mentioned another use on Page 3.

MR. WONG: Can we blow-up what says "neoplastic diseases."

BY MR. WONG:

Q. What is a neoplastic disease?

A. Neoplastic diseases are some kind of diseases that are cancerous, in the sense.

Q. In that sense, what is prednisone indicated for?

A. It's indicated for palliative management of leukemia and lymphomas in adults.

Q. All right. Thank you.

MR. WONG: Let's go to the next slide.

BY MR. WONG:

Q. This is DDX-2100.14.

Doctor, what is listed here on the next slide?

A. The slide lists all the prednisones approved by the FDA.

Q. Right. I forgot to ask you a question.

Going back to that prednisone label on Pages 2 and 3, was there any indication in that prednisone label that it was approved by FDA for anti-cancer effects?

A. No, there was no indication that prednisone was approved as an anti-cancer.

Q. Okay. Sorry. What's listed here now on this slide?
A. So these are the prednisones approved by the FDA. These are brand names of prednisone drugs that are already on the market.
Q. And did you review the labels of each of these drugs?
A. Yes, I did.
Q. And when you reviewed these other labels, what did you find?
A. I found that prednisone has not been approved as an anti-cancer drug.
Q. Okay. Let's talk about combination therapies. To your knowledge, has FDA previously approved the use of prednisone in combination with an anti-cancer drug for treating prostate cancer?
A. No, it has not.
Q. All right. What about in general, whether it has anti-cancer effects or not? In general, has FDA approved prednisone in combination with another drugs in the prostate cancer space?
A. Prednisone in combination --
Q. Let me repeat the question. In general, has FDA previously approved the use of prednisone, in combination with another drug, for treatment of prostate cancer treatment?
A. Yes, it has.
Q. In those approvals, has FDA ever approved the use of

prednisone as an anti-cancer agent specifically in those combinations?

A. No.

Q. What about for Zytiga; did FDA approve the use of prednisone as an anti-cancer agent when it approved Zytiga?

A. No.

Q. Now, Doctor, in forming your opinion in this case, did you familiarize yourselves with the regulatory development and history of Zytiga?

A. Yes, I have.

Q. And did you review the pertinent regulatory documents filed in support of Zytiga's NDA approval?

A. Yes, I have.

MR. WONG: Let's go to the next slide.

BY MR. WONG:

Q. This is a timeline on DDX-2100.15.

Doctor, what is shown here?

A. This slide shows the regulatory timeline for Zytiga, starting from their IND submissions, back in 2005, to all the way to the recent approval, in 2018.

Q. Okay.

A. Yeah.

MR. WONG: Your Honor, we're about to get into some of these documents. I'm not sure what time it is or if it's a good time to break for the day.

THE COURT: As it happens, I have an appointment at five in chambers, so we're going to get five minutes, tops. So if you don't think it makes sense to launch on this new area, let's break for the day.

MR. WONG: Great. Thank you.

THE COURT: And we'll resume at 9 o'clock in the morning.

(Proceedings concluded at 4:55 p.m.)

FEDERAL OFFICIAL COURT REPORTER'S CERTIFICATE

I, **Mary-Jo Monteleone, CCR, CRCR, RPR,** Official Court Reporter of the United States District Court for the District of New Jersey, do hereby certify that the foregoing proceedings are a true and accurate transcript of the testimony as taken stenographically by and before me at the time, place, and on the date hereinbefore set forth.

I further certify that I am neither related to any of the parties by blood or marriage, nor do I have any interest in the outcome of the above matter.

/S/ Mary-Jo Monteleone, CCR, CRCR, RPR 07/25/2018

Official Court Reporter Date